NOTE

This Microfiche meets the quality requirements of the American National Standard for Microfiche of Documents (ANSI PH5.9-1975). However, because of imperfections in the document from which it was made, it contains images that are illegible or difficult to read. The source document for this microfiche is the best copy that could be obtained prior to filming.

CIS

Congressional Information Service
Washington, D.C.

DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR 1991

HEARINGS

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS
HOUSE OF REPRESENTATIVES

ONE HUNDRED FIRST CONGRESS

SECOND SESSION

SUBCOMMITTEE ON THE DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES

WILLIAM H. NATCHER, Kentucky, *Chairman*

NEAL SMITH, Iowa
DAVID R. OBEY, Wisconsin
EDWARD R. ROYBAL, California
LOUIS STOKES, Ohio
JOSEPH D. EARLY, Massachusetts
BERNARD J. DWYER, New Jersey
STENY H. HOYER, Maryland

SILVIO O. CONTE, Massachusetts
CARL D. PURSELL, Michigan
JOHN EDWARD PORTER, Illinois
C. W. BILL YOUNG, Florida
VIN WEBER, Minnesota

MICHAEL A. STEPHENS, ROBERT L. KNISELY, SUSAN E. QUANTIUS, and JOANNE L. ORNDORFF, *Subcommittee Staff*

PART 4A

NATIONAL INSTITUTES OF HEALTH

Page

Overview 1
National Cancer Institute 249
National Heart, Lung, and Blood Institute 539
National Institute of Dental Research 745
National Institute of Diabetes and Digestive and Kidney Diseases 855
National Institute of Neurological Disorders and Stroke 1003
National Institute of Allergy and Infectious Diseases 1129
National Institute of General Medical Sciences 1303

Printed for the use of the Committee on Appropriations

U.S. GOVERNMENT PRINTING OFFICE
28-965O WASHINGTON : 1990

For sale by the Superintendent of Documents, Congressional Sales Office
U.S. Government Printing Office, Washington, DC 20402

H181-41

COMMITTEE ON APPROPRIATIONS

JAMIE L. WHITTEN, Mississippi, *Chairman*

WILLIAM H. NATCHER, Kentucky
NEAL SMITH, Iowa
SIDNEY R. YATES, Illinois
DAVID R. OBEY, Wisconsin
EDWARD R. ROYBAL, California
LOUIS STOKES, Ohio
TOM BEVILL, Alabama
BILL ALEXANDER, Arkansas
JOHN P. MURTHA, Pennsylvania
BOB TRAXLER, Michigan
JOSEPH D. EARLY, Massachusetts
CHARLES WILSON, Texas
LINDY (MRS. HALE) BOGGS, Louisiana
NORMAN D. DICKS, Washington
MATTHEW F. McHUGH, New York
WILLIAM LEHMAN, Florida
MARTIN OLAV SABO, Minnesota
JULIAN C. DIXON, California
VIC FAZIO, California
W. G. (BILL) HEFNER, North Carolina
LES AuCOIN, Oregon
DANIEL K. AKAKA, Hawaii
WES WATKINS, Oklahoma
WILLIAM H. GRAY III, Pennsylvania
BERNARD J. DWYER, New Jersey
STENY H. HOYER, Maryland
BOB CARR, Michigan
ROBERT J. MRAZEK, New York
RICHARD J. DURBIN, Illinois
RONALD D. COLEMAN, Texas
ALAN B. MOLLOHAN, West Virginia
LINDSAY THOMAS, Georgia
CHESTER G. ATKINS, Massachusetts
JIM CHAPMAN, Texas

SILVIO O. CONTE, Massachusetts
JOSEPH M. McDADE, Pennsylvania
JOHN T. MYERS, Indiana
CLARENCE E. MILLER, Ohio
LAWRENCE COUGHLIN, Pennsylvania
C. W. BILL YOUNG, Florida
RALPH REGULA, Ohio
VIRGINIA SMITH, Nebraska
CARL D. PURSELL, Michigan
MICKEY EDWARDS, Oklahoma
BOB LIVINGSTON, Louisiana
BILL GREEN, New York
JERRY LEWIS, California
JOHN EDWARD PORTER, Illinois
HAROLD ROGERS, Kentucky
JOE SKEEN, New Mexico
FRANK R. WOLF, Virginia
BILL LOWERY, California
VIN WEBER, Minnesota
TOM DELAY, Texas
JIM KOLBE, Arizona
DEAN A. GALLO, New Jersey

FREDERICK G. MOHRMAN, *Clerk and Staff Director*

DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR 1991

MONDAY, MARCH 12, 1990.

NATIONAL INSTITUTES OF HEALTH—OVERVIEW

WITNESSES

DR. WILLIAM F. RAUB, ACTING DIRECTOR, NATIONAL INSTITUTES OF HEALTH

DR. KATHERINE L. BICK, DEPUTY DIRECTOR FOR EXTRAMURAL RESEARCH, NIH

JOHN D. MAHONEY, ASSOCIATE DIRECTOR FOR ADMINISTRATION, NIH

DR. LEAMON M. LEE, DIRECTOR, DIVISION OF FINANCIAL MANAGEMENT

DR. ANTHONY S. FAUCI, DIRECTOR, NIAID, AND ASSOCIATE DIRECTOR FOR AIDS RESEARCH, NIH

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

OPENING REMARKS

Mr. NATCHER. At this time we take up the budget request for the fiscal year 1991 for the National Institutes of Health.

We have before the committee, Dr. Raub, along with a number of other heads of the National Institutes, the Directors, and their assistants.

Dr. Raub, several days go we had overview hearings on the entire budget for fiscal year 1991. Before our full committee of 57 members, we had the Secretary of the Treasury, the Director of OMB, and the Chairman of the Joint Economic Council. At that time, Dr. Raub, I said to those gentlemen in attendance that if I had made the selection for the man of the decade on the magazine cover of Time Magazine, I would not have selected Gorbachev.

The Director of OMB said out loud, which one of the Directors of NIH would you select?

My friend, Joe Early was there. Which one would you select? I said to him that I could select eight or ten men and women—not only Directors at NIH, but people who down through the years have served NIH with honor and distinction.

But, Dr. Raub, I am sincere about that. All down through the years that is the way I have felt. You all know how my friend Joe Early feels. You don't have a better friend anywhere in the United States than Joe Early. That is the way we feel on this committee. We are proud of all of you. If I could say that about all the other agencies and departments of the Federal Government, we would have the most perfect government in the world. I cannot say it about all of them, but I can say it about you all. We are delighted to have you before us.

Dr. Raub, before you give your statement, tell us who you have with you at the table.

Dr. RAUB. Thank you very much, Mr. Chairman. It is always a pleasure to tell you about the programs of the National Institutes of Health. I speak for my colleagues in saying that we would rather have the recognition from you than Time Magazine any time, sir.

We have here Dr. Katherine Bick, Deputy Director for Extramural Research; John Mahoney, Associate Director for Administration; Dr. Leamon Lee, Director of the Division of Financial Management; Dr. Anthony S. Fauci, Director of the National Institute of Allergy and Infectious Diseases, and Associate Director for AIDS Research; and Mr. Dennis Williams, Deputy Assistant Secretary, Budget, DHHS.

Mr. NATCHER. Thank you very much. Now we will be pleased to hear from you.

Dr. RAUB. Mr. Chairman, I have a statement which, with your permission, I will submit for the record.

Mr. NATCHER. It will be included in its entirety.

CYSTIC FIBROSIS

Dr. RAUB. As indicated in the statement, and the collective testimony that you will be hearing over the next several days, the National Institutes of Health can point to many achievements over the last year. I will highlight only one in the interest of time, the progress against cystic fibrosis, a fatal disease of children and young adults. One of the manifestations is thick mucous in the lungs, causing difficulty in breathing, and harboring bacteria that produce life-threatening infections.

The cystic fibrosis gene occurs in one out of 20 Caucasians and one out of every 2,000 births. Within the last year, the cystic fibrosis gene has been found by grantees in the National Institute of Diabetes and Digestive and Kidney Diseases and the National Heart, Lung and Blood Institute. Those scientists also received contributions from the Howard Hughes Medical Institute and the Cystic Fibrosis Foundation.

Since the discovery of the gene, progress has been fast-paced. The gene has been sequenced. The product has been identified; it turns out to be a protein of cell membranes involved in the transport of chlorodine. The discovery leads to improved screening tests and genetic counseling as well as drug therapies that might block, and others that might ultimately prevent, cystic fibrosis. Similar scenarios are playing out in various stages of research on other diseases. The prospects for this kind of progress are very bright with about 4,000 genetic diseases already known.

At the same time that this extraordinary work in molecular biology was underway, clinical scientists were making other inroads. Scientists funded by the National Heart, Lung and Blood Institute demonstrated a drug that makes the mucous less viscous. It eases breathing, reduces risk of infection, and decreases the morbidity associated with the disease, and increases life span.

Similar examples of successful clinical research with applications here and now are emerging from every one of our institutes. I believe this example illustrates the balance of our investments with a focus on payoffs for today and creating new promises for tomorrow.

FEATURES OF FY 1991 BUDGET REQUEST

Turning to our request for fiscal year 1991, I call your attention to several features:

First, we present a budget designed to maintain a strong effort across a broad front with a balanced effort in basic and targeted research, laboratory and clinical investment. There is emphasis, as always, on basic research and that is manifest in the proposed funding increase for research project grants and intramural research.

The budget proposes to continue our strong assault on AIDS buoyed as it is, by the successes in drug therapy.

It calls for an expansion of the human genome project and the effort to attract minorities and others to research careers covering a spectrum from high school to post-graduate and gives emphasis to repairing and refurbishing the buildings and the facilities that serve the NIH intramural program.

The last item emerges as the most important one in this request, because our buildings and facilities issue presents our most urgent problems.

First, we are concerned about ensuring the safety for patients and staff in our clinical center and the safety for scientists and support personnel in our laboratories and related facilities. We are anxious to avoid inefficiencies and costly shutdowns associated with obsolete and overtaxed utility systems.

We want to be sure that facilities for laboratory animals conform to the letter and spirit of the applicable regulations and guidelines.

Last, and hardly the least, we want to be able to enable our scientists to address needs that are beyond the capabilities of buildings and support systems dating back to the 1940s and 1950s. We expect to be grappling with the problems of our research infrastructure and physical plant for at least the next decade.

Mr. Chairman, we are living through a time of extraordinary progress and prospects for biomedical science. NIH is privileged to be at the forefront of that enterprise, thanks to the strong support from a succession of Congresses and Presidents. We continue to see the investments yield a high return in terms of new scientific knowledge and better health for people everywhere.

On behalf of the NIH, I present a budget request of $7,929,686,000 for fiscal year 1991. my colleagues and I will be happy to respond as best we can to your questions.

[The statement of Dr. Raub follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director

Mr. Chairman, it is my privilege to appear before you and your colleagues on the Subcommittee to present the President's FY 1991 budget proposal for the National Institutes of Health. In my presentation I will describe some of the advances made during the past year, discuss briefly a few significant new programs, mention some current issues, and outline the key points of the FY 1991 budget proposal.

In subsequent testimony Directors of our constituent units will describe in detail a number of important accomplishments, but I will take the liberty now of citing briefly a few highlights. For example:

- Last year, a team from the National Cancer Institute (NCI) and the National Heart, Lung, and Blood Institute (NHLBI) transferred cells containing foreign genes into humans for the first time. This successful use of a tracer gene not only is the first application of a powerful new tool for research but also constitutes a major step toward gene therapy in humans.
- Scientists at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) have determined the strictire of the receptor, a protein on the surface of most cells and basal cells that plays a central role in allergic reactions. From this information the scientists have developed a tissue culture system that can be used to screen for a new class of drugs, possibly for the prevention of allergy attacks.
- Grantees of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and of NHLBI have isolated the cystic fibrosis (CF) gene. This step enhances significantly the prospects for developing drugs that can be designed to correct the defect.
- Polymerase chain reaction (PCR), a powerful new technique developed directly from basic research funded by NIH, is now used in many areas of research and service. It is expected to have a profound effect on the joint effort by the NIH and the Department of Energy (DOE) to map and sequence the genome of humans and other organisms. PCR is the cornerstone of a proposal to "translate" the information from various physical mapping methods into a common language known as sequence-tagged-sites (STS). These sites are short tracts of a unique DNA sequence that can be identified by PCR and that can act as landmarks on a physical map.

During 1989 the NIH continued to lead the Federal Government's research efforts against AIDS through studies conducted by our intramural scientists, by grantees, and by contractors. Studies sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) have shown that the drug AZT can delay disease progression in HIV-infected persons with low counts of T4 cells whether they have AIDS symptoms or not. These studies indicate that an estimated 600,000 HIV-infected Americans with early or no symptoms of the disease could benefit from AZT treatment. Another study has shown that reduced dosages of AZT are effective and reduce side effects. The efficacy and toxicity of a promising new drug, dideoxyinosine (ddI), will soon be compared with AZT in a large study.

The NIAID has established 18 AIDS treatment research programs based in the communities where people with AIDS live and receive their medical care. The program will reach increased numbers of persons with HIV infection, including those in population groups that have been underrepresented in AIDS studies.

The accelerated pace and productivity of basic biomedical research, so characteristic of its recent history, continues unabated. There has been a marked shortening of the interval between new findings from basic studies and their widespread application in measures for improving the health of the American people.

The NIH intramural program is recognized as a leader among government agencies in implementing the Technology Transfer Act of 1986, whose purpose is to facilitate the transfer of the results of federally supported research through development and then through widespread use. The NIH now has about 100 Cooperative Research and Development Agreements (CRADAs) with industry and about that many more in various stages of negotiation. Through the CRADAs, government and industry scientists can make optimum use of the resources unique to each party in their joint research efforts.

The National Center for Biotechnology Information (NCBI), established at NIH in late 1988 within the National Library of Medicine, has begun to integrate existing databases and is developing new computer programs to analyze them. Information access has become an urgent problem, not only for the human genome program, but also for the many facets of biotechnology.

While we extend our efforts in technology transfer, we must ensure that research goals are not unduly influenced by conflicts of interest affecting the participants in research projects at awardee institutions. We seek balanced solutions that will protect the integrity of the supported research without imposing unnecessary restrictions on this creative enterprise.

We also face concerns about dishonest practices in biomedical science. Misconduct in science is rare, but when it occurs it undermines the public's faith and can jeopardize subsequent research and even proper medical treatment. To monitor and investigate all misconduct in science cases in the Public Health Service--which includes any on the NIH campus or at awardee institutions--the Office of Scientific Integrity (OSI) was established within the Office of the Director, NIH. It currently is dealing with 72 active cases. The OSI will collaborate with the

Office of Scientific Integrity Review (OSIR) that recently was established in the Office of the Assistant Secretary for Health.

In another area of concern, I note with alarm the continuing attacks on biomedical science by advocates of animal rights. At a time when biomedical research is making such rapid progress and its benefits are ever more promising, it is tragic that animal "rights" activists continue to intensify their efforts to stifle important avenues of research through harassment of individual scientists and blatant terrorist acts of theft and property destruction. We at the NIH believe that the use of laboratory animals is a scientific necessity and, in fact, is an ethical imperative. We are greatly concerned about the humane care and use of animals and strongly believe that good animal care is an indispensable part of good science.

Mr. Chairman, the FY 1991 budget request for the NIH is $7,929.7 million, an increase of $353.3 million or 4.7 percent over the comparable FY 1990 level. The requested increase includes an additional $56.6 million for the AIDS program and $48.5 million for the Human Genome Initiative. The budget request continues to reflect the priority the Administration places on the support of basic research, seeking an increase of 5.7 percent.

In allocating the FY 1991 request, NIH gave its highest priority to the support of improvements in its intramural facilities, whose needs have become critical in recent years. Of particular importance is continued support for ongoing modernization of the Warren Grant Magnuson Clinical Center, for renovation projects in our laboratory buildings and the upgrading of our animal facilities. Furthermore, the condition of NIH boilers, chillers, and steam lines has reached the critical point where the useful life of these vital facilities is ending. The NIH firmly believes that these needs must be addressed and has requested $88.6 million, an increase of $27.6 million over the FY 1990 funding level for the building and facilities fund.

Investigator-initiated research continues to be a very high priority. Research project grants would be funded at a level of $4,425 million, an increase of 5.4 percent over the FY 1990 funding level. This amount will allow average cost increases of about 5.8 percent for noncompeting and 2.0 percent for competing awards. The FY 1991 request would support a total of 20,439 research project grants, of which 5,095 would be competing research project grants, an increase of 462 competing awards over the FY 1990 level.

The NIH also continues to place a high priority on research training. The FY 1991 request will support a total of 12,020 trainees, an increase of 225 over the FY 1990 level.

As a reflection of the importance NIH places on expanding the number of biomedical researchers who are ethnic minorities, the FY 1991 budget requests that the Minority Access to Research Careers Program, the Minority Biomedical Research Support Program, the Minority High School Apprenticeship Program, and the Research Centers in Minority Institutions receive an overall 17 percent increase over FY 1990.

In FY 1991 the Biomedical Research Support Grant Program will be funded at a level of $17.7 million. Consistent with the Secretary's minority health initiative, one third of the FY 1991 funds will be awarded to institutions to increase support for under-represented minorities or economically disadvanted students in science and engineering.

The Intramural Research Program at NIH constitutes the nation's preeminent institution for the biomedical sciences. The request for intramural research of $914.9 million provides an increase for intramural research of 6.9 percent over the FY 1990 base. This increase allows for continuing-expansion in the AIDS program and will cover the costs of such administrative items as within-grade increases and the costs associated with January, 1990 and 1991 pay raises.

The request also includes $20 million for the Director's Discretionary Fund. Although Congress did not support this fund in the FY 1990 appropriations, NIH believes it is an important mechanism that will allow the NIH to be more responsive to emerging research opportunities.

For the first time, a separate request is made for the recently established new National Center for Human Genome Research, and it proposes a significant increase, continuing the emphasis placed on this initiative by the Administration. A five-year plan to be released in the spring of 1990 establishes the scientific goals for the U.S. human genome project from 1991 to 1995. The FY 1991 request for the Center is $108 million, an increase of $48.5 million over the comparable FY 1990 estimate. The successful completion of this project holds great promise for future advances in health research.

I would be pleased to respond to any questions you may have.

PRIVATE VS. PUBLIC FUNDING

Mr. NATCHER. Thank you, Doctor. As you and your colleagues know, private and public spending for health research have increased rapidly during the last ten years—from just over $7 billion a year in 1979 to just under $21 billion in 1989. The portion of this research funded by NIH, however, declined from 41 percent to just under 30 percent. Does the large increase in private funding for biomedical research indicate that the NIH needs to modify the basic approach to these research needs?

Dr. RAUB. No, Mr. Chairman. We don't believe that it requires any change in our fundamental approach. Overall, we welcome the appearance of funds from other sources, thinking that the national effort will be more healthy and more stable if there are multiple sources of support. However, we must continue to focus our attention on our interactions with other foundations and sources of private support as well as with the emerging new connections with the private sector.

We believe by continuing our good communications with those various sectors and being attentive to the changes in funding opportunities and priorities, that we will be able to ensure that the National Institutes of Health is a part of this enterprise, is as strong as ever, and that there is overall benefit from these emerging sources of funds.

NIH DIRECTOR

Mr. NATCHER. Dr. Raub, as you know, you have been at NIH now for almost 25 years, including eight months as its Acting Director. When the new Director comes on board, what will you tell him, Doctor, are some of to the major problems he will have to bare? What will you say to him?

Dr. RAUB. I put those issues in three distinct categories, Mr. Chairman:

First and foremost is the issue of recruitment and retention of world class scientists and other staff to ensure that the National Institutes of Health of the future is at least equal to the National Institutes of Health of the past. Salaries are a critical part of that, but not the whole story. In addition to providing competitive compensation, we must also ensure that we are doing everything possible to facilitate the work of scientists and staff. That means strong facilities and support services, clear priorities for resource allocation, and whenever possible, the reduction or elimination of unproductive administrative requirements.

The second area I would call for his or her attention is that of maintaining public confidence in NIH in particular, and in science in general. We must continue to fight the erosion in that confidence that follows in the wake of alleged misconduct in science, concerns over the use of laboratory animals, concerns for protection of human subjects and the issues surrounding the new relationships between industry and academia as well as industry and NIH.

At the same time, we need to do more and reach out more to the public, offering better accountability to the public for what their tax dollars mean when transformed into NIH programs, as well as helping the public understand science itself better.

The third category would be program balance, harmonizing the many different ideas and needs associated with our various programs; issues of research project grants, research centers, intramural research, research training, and the balance between basic and targeted efforts. It is that class of issues that I believe will present formidable challenges to the next director.

NEW INSTITUTES

Mr. NATCHER. At the present time there are several proposals being discussed which, if enacted into law, would create new institutes. Through the years, our committee has not advocated a lot of these proposals which would create new institutes. Dr. Mason was here the other day. Dr. Mason stated that in his opinion, NIH has been hurt by some of their new institutes and new centers. How do you feel about that, Dr. Raub?

Dr. RAUB. Traditionally, as you know, Mr. Chairman, we have viewed the prospect of new institutes with caution, concerned in most instances that there will be an increase in administrative costs, at least short term, that will outweigh whatever gains might come about from the new organizational focus. I believe history shows that in some instances those concerns were well placed and in other instances, over the long haul, the early disadvantages were overcome by stronger and more vibrant, broad-based programs.

I think we will continue to approach every new proposal with that cautionary view, to be sure that where there are research needs and opportunities that are not being addressed, that we array ourselves as appropriate to meet those, either through organizational changes or renewed emphasis within the current structure.

FY 1991 BUDGET INCREASES

Mr. NATCHER. The President's budget includes $353 million increase for the National Institutes of Health. If you subtract from this amount increases for AIDS and human genome activities, the increase for the rest is only $275 million, or a little over three percent.

Doctor, in your opinion, is this enough money to maintain current program levels?

Dr. RAUB. Activities other than the AIDS and genome effort fall under projected inflationary costs, nevertheless we believe that with a strict setting of priorities we can maintain strong programs and ensure that we are meeting as many of the opportunities as possible.

CURRENT SERVICES

Mr. NATCHER. What is NIH's estimate of the amount which would need to be added to the President's request just to maintain current services?

Dr. RAUB. We calculate that number to be approximately $460,000,000.

FUNDING HISTORY

Mr. Natcher. Dr. Raub, we will insert in the record at this point a series of history table which your staff prepared for the committee each year.

[The information follows:]

DHHS-National I .tes of Health
Appropriation History

CURRENT AND CONSTANT DOLLARS 1/

(Dollars in Thousands)

	Includes AIDS				Excludes AIDS			
	Current Dollars	Percent Change	Constant Dollars	Percent Change	Current Dollars	Percent Change	Constant Dollars	Percent Change
1982............	$3,641,875	---	$3,641,875	---	$3,638,520	---	$3,638,520	---
1983............	4,023,969	10.5	3,860,663	6.0	4,002,301	10.0	3,839,874	5.5
1984............	4,493,588	11.7	4,153,423	7.6	4,449,467	11.2	4,112,642	7.1
1985............	5,149,459	14.6	4,617,094	11.2	5,085,722	14.3	4,559,959	10.9
1986	5,498,454	6.8	4,801,711	4.0	5,363,787	5.5	4,684,121	2.7
1987............	6,182,910	12.4	5,239,754	9.1	5,922,003	10.4	5,018,647	7.1
1988............	6,666,693	7.8	5,482,478	4.6	6,193,408	4.6	5,093,263	1.5
1989............	7,144,764	7.2	5,638,229	2.8	6,542,470	5.6	5,162,934	1.4
1990 Estimate...	7,576,352	6.0	5,748,806	2.0	6,832,820	4.4	5,184,627	0.4
1991 Estimate...	7,929,686	4.7	5,774,183	0.4	7,129,522	4.3	5,191,526	0.1

1/ Constant dollars are based on Implicit Price Deflators for the GNP.

DHHS-NATIONAL .ES OF HEALTH

RESEARCH PROJECT GRANTS

TOTAL NUMBER OF AWARDS AND DOLLARS
Includes AIDS

(Dollars in thousands)

	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990 Estimate	1991 Estimate
No. of Awards:											
Competing.....	5109	5027	5309	5493	6246	6211	6453	6213	5382	4633	5095
Total.........	16480	15970	16921	17305	18357	18796	19583	20202	20681	20316	20439
Cost of Awards:											
Competing.....	$545,036	$564,620	$643,396	$731,916	$918,099	$930,274	$1,129,836	$1,098,538	$982,433	$943,345	$1,058,514
Total.........	1,766,640	1,832,867	2,095,116	2,309,553	2,769,099	2,922,221	3,463,578	3,739,855	4,033,421	4,197,957	4,424,775
Average Cost:											
Competing.....	$106.7	$112.3	$119.4	$133.2	$147.0	$149.8	$175.1	$176.8	$182.5	$203.6	$207.8
Total.........	107.2	114.8	123.8	138.1	150.9	155.5	176.9	185.1	195.0	206.6	216.5
Percent increase over prior year:											
Competing.....		5.3	6.3	11.6	10.3	1.9	16.9	1.0	3.2	11.5	2.0
Total.........		7.1	7.9	11.5	9.3	3.0	13.8	4.7	5.4	5.9	4.8
Average Length of Award.....		3.3	3.3	3.4	3.4	3.6	3.9	4.1	4.2	4.3	4.3

NOTE: Data from FY 1981-1989 reflects actual obligations. FY 1987 and 1988 are adjusted to reflect transfer of AIDS funding from the Office of the Director to NIGMS thereby changing the number of grants.

DHHS-National Institutes of Health

HISTORY OF CONGRESSIONAL APPROPRIATIONS, 1981-1991 ESTIMATE

INCLUDES AIDS

(Dollars in thousands)

	1981 1/	1982 1/	1983 2/	1984	1985	1986 3/	1987 4/	1988 5/	1989 6/	1990 Estimate 7/	1991 Estimate
NCI	$989,355	$986,617	$987,642	$1,081,581	$1,183,806	$1,257,237	$1,402,837	1,469,327	1,572,879	1,634,294	1,694,059
NHLBI	549,693	559,637	624,259	704,939	805,269	859,239	930,001	965,536	1,046,259	1,072,335	1,112,502
NIDR	71,114	71,983	79,292	88,674	100,688	103,282	117,945	126,297	131,026	135,744	140,520
NIADDK	369,462	368,191	413,492	464,026	543,576	569,340	511,124	534,733	559,886	581,466	605,349
NINCDS	252,533	265,901	297,064	335,883	396,885	433,362	490,233	534,692	472,662	490,396	512,212
NIAID	232,077	235,895	279,129	319,596	370,965	383,452	545,523	638,455	743,870	832,960	886,875
NIGMS	333,764	339,862	369,813	415,937	482,260	514,765	570,916	638,176	683,920	712,030	745,494
NICHD	220,628	226,309	254,324	276,046	313,295	321,796	366,780	396,811	425,918	442,906	461,473
NEI	117,983	127,374	141,901	155,131	181,678	195,094	216,637	224,947	231,404	236,529	247,392
NIEHS	93,491	106,270	164,867	180,597	194,819	197,478	209,294	215,666	223,686	229,233	235,792
NIA	75,608	81,903	93,996	115,292	144,521	156,491	177,681	194,746	222,888	239,452	248,938
NIAMS	---	---	---	---	---	---	138,713	147,679	160,080	168,927	176,080
NIDCD	---	---	---	---	---	---	---	---	94,687	117,582	122,847
DRR	175,627	184,177	213,917	243,177	304,025	305,667	322,860	368,153	340,898	337,105	319,151
NCNR	---	---	---	---	---	---	20,000	23,380	29,195	33,513	35,127
NCHGR	---	---	---	---	---	---	---	---	28,230	59,538	108,029
FIC	9,124	9,205	10,147	11,336	11,728	11,551	11,420	15,651	14,164	15,656	16,355
Subtotal, IRD's	3,490,459	3,563,324	3,929,843	4,392,215	5,033,515	5,308,754	6,031,964	6,494,249	6,981,652	7,339,666	7,668,195
NLM	44,666	45,035	51,943	49,613	55,910	57,808	61,838	67,910	77,883	85,728	89,916
OD	22,531	23,618	24,683	26,720	38,304	116,992	57,208	56,664	46,737	89,916	82,975
B & F	11,750	9,898	17,500	25,040	21,730	14,900	31,900	47,870	38,492	61,042	88,600
TOTAL, NIH	3,569,406	3,641,875	4,023,969	4,493,588	5,149,459	5,498,454	6,182,910	6,666,693	7,144,764	7,576,352	7,929,686

1/ No enacted appropriation. Authorized under a continuing resolution.
2/ Reflects transfer of National Toxicology Program between NCI and NIEHS.
3/ Reflects administrative reduction of $3,000.
4/ The Arthritis Institute and the National Center for Nursing Research established in FY 1987.
5/ The Institute on Deafness and Other Communication Disorders was established in FY 1988.
6/ National Center for Human Genome Research was established in FY 1989. Reflects AZT transfer of $7,443 and administrative reduction of $1,852.
7/ Reflects sequester amount of $96,570 and administrative reductions in the amount of $24,428.

DHHS-National Institutes of Health

NIH/DFM/BFPB
Feb-21-1990

HISTORY OF CONGRESSIONAL APPROPRIATIONS, 1981-1991 ESTIMATE

EXCLUDES AIDS

(Dollars in thousands)

	1981	1982 2/	1983	1984	1985	1986 3/	1987 4/	1988 5/	1989 6/	1990 Estimate	1991 Estimate
NCI...............	$989,355	$984,217	$977,852	$1,064,954	$1,156,932	$1,212,187	$1,339,082	$1,379,383	$1,448,731	$1,483,990	$1,533,252
NHLBI.............	549,693	559,632	623,057	700,068	795,946	843,771	912,757	940,651	1,007,648	1,030,279	1,068,039
NIDR..............	71,114	71,958	79,267	88,593	100,591	101,570	114,698	122,447	126,885	131,082	135,518
NIADDK............	369,462	368,191	413,492	464,026	543,576	569,340	510,629	531,403	556,210	576,146	599,558
NINCDS............	252,533	265,870	296,380	334,373	395,717	431,927	486,548	446,659	459,230	474,238	494,985
NIAID.............	232,077	235,598	269,906	299,980	347,692	320,176	399,763	415,157	430,982	439,002	463,468
NIGMS.............	333,764	339,862	369,813	415,937	482,260	514,765	565,496	630,452	673,019	697,416	730,007
NICHD.............	220,628	226,309	254,324	276,046	313,295	320,396	362,018	379,658	403,214	416,157	432,463
NEI...............	117,983	127,341	141,856	155,071	181,478	194,998	216,384	221,117	226,439	230,996	241,505
NIEHS.............	93,491	106,270	164,867	180,597	194,819	197,478	209,078	211,770	219,489	224,942	231,212
NIA...............	75,608	81,903	93,996	115,292	144,521	156,491	177,497	194,385	222,386	238,593	248,009
NIAMS.............	---	---	---	---	---	---	138,613	147,118	159,347	167,689	174,597
NIDCD.............	---	---	---	---	---	---	---	75,691	94,687	117,582	122,269
DRR...............	175,627	183,613	213,218	241,821	301,223	299,510	311,833	315,935	295,688	291,009	270,772
NCNR..............	---	---	---	---	---	---	20,000	22,778	28,434	32,526	33,979
NCHGR.............	---	---	---	---	---	---	---	---	28,230	59,538	108,029
FIC...............	9,124	9,205	10,147	11,336	11,728	11,551	11,420	11,146	9,510	10,758	11,148
Subtotal, IRD's...	3,490,459	3,559,969	3,908,175	4,348,094	4,969,778	5,174,160	5,775,816	6,045,750	6,390,129	6,621,943	6,898,810
NLM.,.............	44,666	45,035	51,943	49,613	55,910	57,808	61,838	67,910	77,804	85,235	89,384
OD................	22,531	23,618	24,683	26,720	38,304	116,919	52,449	51,028	40,945	79,365	69,228
B&F...............	11,750	9,898	17,500	25,040	21,730	14,900	31,900	28,720	33,592	46,277	72,100
TOTAL, NIH...	3,569,406	3,638,520	4,002,301	4,449,467	5,085,722	5,363,787	5,922,003	6,193,408	6,542,470	6,832,820	7,129,522

1/ No enacted appropriation. Authorized under a continuing resolution.
2/ Reflects transfer of National Toxicology Program between NCI and NIEHS.
3/ Reflects administrative reduction of $3,000.
4/ The Arthritis Institute and the National Center for Nursing Research established in FY 1987.
5/ The Institute on Deafness and Communication Disorders was established in FY 1988.
6/ The National Center for Human Genome Research was established in 1989.

DHHS-National Institutes of Health

HISTORY OF CONGRESSIONAL APPROPRIATIONS, 1981-1991 ESTIMATE

AIDS

(Dollars in thousands)

	1981	1982 1/	1983 2/	1984	1985	1986 3/	1987 4/	1988 5/	1989	1990 Estimate	1991 Estimate
NCI...............	---	$2,400	$9,790	$16,627	$26,874	$45,050	$63,755	$89,944	$124,148	$150,304	$160,807
NHLBI.............	---	5	1,202	4,871	9,323	15,468	17,244	24,885	38,611	42,056	44,463
NIDR..............	---	25	25	81	97	1,712	3,247	3,850	4,141	4,662	5,002
NIADDK............	---	---	---	---	---	---	495	3,330	3,676	5,320	5,791
NINCDS............	---	31	684	1,510	1,168	1,435	3,685	12,342	13,432	16,158	17,227
NIAID.............	---	297	9,223	19,616	23,273	63,276	145,760	223,298	312,888	393,958	423,407
NIGMS.............	---	---	---	---	---	---	5,420	7,724	10,901	14,614	15,487
NICHD.............	---	---	---	---	---	1,400	4,762	17,153	22,704	26,749	29,010
NEI...............	---	33	45	60	200	96	253	3,830	4,965	5,533	5,887
NIEHS.............	---	---	---	---	---	---	216	3,896	4,197	4,291	4,580
NIA...............	---	---	---	---	---	---	184	361	502	859	929
NIAMS.............	---	---	---	---	---	---	100	561	733	1,238	1,483
NIDCD.............	---	---	---	---	---	---	---	---	---	---	578
DRR...............	---	564	699	1,356	2,802	6,157	11,027	52,218	45,210	46,096	48,379
NCNR..............	---	---	---	---	---	---	---	602	761	987	1,148
FIC...............	---	---	---	---	---	---	---	4,505	4,654	4,898	5,207
	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------
Subtotal, IRD's...	0	3,355	21,668	44,121	63,737	134,594	256,148	448,499	591,523	717,723	769,385
NLM...............	---	---	---	---	---	---	---	---	79	493	532
OD................	---	---	---	---	---	73	4,759	5,636	5,792	10,551	13,747
B & F.............	---	---	---	---	---	---	---	19,150	4,900	14,765	16,500
	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------
TOTAL, NIH........	0	3,355	21,668	44,121	63,737	134,667	260,907	473,285	602,294	743,532	800,164

1/ No enacted appropriation. Authorized under a continuing resolution.

2/ Reflects transfer of National Toxicology Program between NCI and NIEHS.

3/ Reflects administrative reduction of $3,000.

4/ The Arthritis Institute and the National Center for Nursing Research established in FY 1987.

5/ The Institute on Deafness and Other Communication Disorders was established in FY 1988.

DHHS-NAT NSTITUTES OF HEALTH
Research Centers

TOTAL AWARDS
Includes AIDS

(Dollars in thousands)

	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990 Estimate	1991 Estimate
NCI.............	57	58	60	59	58	59	60	60	56	56	56
NHLBI...........	60	59	56	57	60	60	60	65	64	64	64
NIDR............	8	8	8	11	13	16	13	16	19	21	21
NIDDK...........	39	38	45	40	45	31	37	38	40	40	40
NINCDS..........	33	30	30	38	40	38	38	29	29	29	29
NIAID...........	20	18	18	18	18	17	16	22	27	16	16
NIGMS...........	22	23	18	18	15	13	14	16	10	9	9
NICHD...........	43	43	42	42	43	44	44	44	46	53	53
NEI.............	27	27	28	27	28	29	30	29	29	30	30
NIEHS...........	14	11	12	12	15	15	15	16	16	17	17
NIA.............	1	1	1	7	12	12	14	13	18	24	24
NIAMS...........	--	--	--	--	--	14	23	25	26	26	26
NIDCD...........	--	--	--	--	--	--	--	9	9	14	14
DRR.............	157	163	162	166	185	183	183	190	206	196	199
NCNR............	--	--	--	--	--	--	--	--	4	4	4
NCHGR...........	--	--	--	--	--	--	--	--	--	3	9
FIC.............	1	1	1	1	1	1	1	1	--	--	--
TOTAL...........	482	480	481	496	533	532	548	573	599	625	634
Average Cost per Center........	$707.2	$727.3	$776.2	$863.7	$893.0	$891.5	$957.5	$983.9	$1,010.2	$1,015.9	$1,056.2

DHHS-NATIONAL INSTITUTES OF HEALTH
Research Training

TOTAL NUMBER OF TRAINEES
Includes AIDS

(Dollars in thousands)

	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990 Estimate	1991 Estimate
NCI..........	1,531	1,498	1,483	1,465	1,464	1,394	1,475	1,456	1,428	1,403	1,403
NHLBI........	1,634	1,602	1,626	1,688	1,709	1,633	1,666	1,655	1,628	1,624	1,624
NIDR.........	283	203	221	221	197	192	225	224	189	215	215
NIDDK........	887	965	916	977	1,046	764	915	916	825	895	895
NINDS........	497	507	576	565	623	581	653	544	546	528	528
NIAID........	483	462	479	494	518	487	491	561	579	670	670
NIGMS........	3,921	3,679	3,713	3,581	3,396	3,238	3,566	3,587	3,702	3,870	4,006
NICHD........	571	626	671	656	702	728	736	723	640	690	690
NEI..........	231	223	219	222	220	232	229	252	251	254	254
NIEHS........	462	446	459	448	483	446	462	480	434	459	459
NIA..........	163	160	170	161	227	263	313	344	387	385	385
NIAMS........	---	---	---	---	---	223	242	238	219	225	225
NIDCD........	---	---	---	---	---	---	---	96	105	122	122
DRR..........	32	35	37	36	39	36	41	67	73	75	75
NCNR.........	---	---	---	---	---	153	167	186	219	245	245
NCHGR........	---	---	---	---	---	---	---	---	---	135	224
TOTAL........	10,695	10,406	10,570	10,514	10,624	10,370	11,181	11,329	11,225	11,795	12,020
Average cost per FTTP...	$16.4	$14.5	$15.6	$15.8	$20.5	$20.5	$20.8	$21.1	$22.8	$24.3	$24.3

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

Includes AIDS

Paylines for Competing Research Project Grants (FY 1980 - FY 1988)

"Percentile Paylines" for Competing Research Project Grants (FY 1989 - FY 1991)

	ACTUAL										Estimates	
	P A Y L I N E S									P E R C E N T I L E S		
	1980	1981	1982	1983	1984 1/	1985 1/	1986 1/	1987 1/	1988 1/	1989 Actual	1990 Estimate	1991 Estimate
NCI...........	218	197	183	181	184	172	165	165	158	22.6	18	21
NHLBI.........	206	208	196	195	181	177	156	157	155	23.8	14	16
NIDR..........	230	225	213	208	210	195	187	186	194	24.2	12	14
NIDDK.........	221	202	180	184	175	173	165	169	170	24.6	17	20
NINDS.........	232	206	189	185	169	157	159	169	170	30.1	17	19
NIAID.........	204	178	162	166	167	159	158	181	169	27.3	16	14
NIGMS.........	219	193	175	170	163	165	160	154	151	23.0	14	18
NICHD.........	200	196	187	179	170	162	161	164	156	21.1	14	16
NEI...........	232	212	203	201	193	198	192	187	219	39.5	34	31
NIEHS.........	217	247	226	220	224	203	181	175	166	30.3	25	22
NIA...........	227	213	208	190	179	202	189	198	182	29.8	23	21
NIAMS.........	--	--	--	--	--	--	155	147	149	20.7	14	14
NIDCD.........	--	--	--	--	--	--	--	--	170	27.9	28	25
NCNR..........	--	--	--	--	--	--	223	197	174	25.8	18	11
NCHGR.........	--	--	--	--	--	--	--	--	--	39.3	26	30

1/ NHLBI and NICHD use percentiles for making funding decisions. Their priority scores are derived from the percentile score listings in an analogous manner.

NOTES:
1) Paylines for FY 1980 - FY 1988 actuals represent the 90th percentile priority score based on the number of funded research projects. For FY 1989 - 1991, "percentile paylines" were used.
2) 1983-1988 includes the Small Business Innovation Research (SBIR) grants. 1989 - 1991 (years in which percentile method used) exclude SBIR grants.
3) The National Institute on Deafness and Other Communication Disorders (NIDCD) was established in FY 1989.
4) The National Center for Human Genome Research (NCHGR) was established in FY 1990.

DHHS-NATIONAL INSTITUTES OF HEALTH

SUMMARY-NIH

Number of Competing Research Project Grants

YEAR	NUMBER REVIEWED	NUMBER APPROVED	NUMBER ELIGIBLE	NUMBER FUNDED	APPROVAL RATE	SUCCESS RATE	AWARD RATE
1982..........	16,989	14,396	14,479	5,027	84.7%	29.6%	34.7%
1983..........	16,798	14,425	14,482	5,389	85.9%	32.1%	37.2%
1984..........	16,901	14,672	14,738	5,493	86.8%	32.5%	37.3%
1985..........	18,674	16,661	16,762	6,246	89.2%	33.4%	37.3%
1986..........	19,336	17,177	17,218	6,211	88.8%	32.1%	36.1%
1987..........	18,471	16,748	16,838	6,453	90.7%	34.9%	38.3%
1988..........	19,205	17,593	17,621	6,213	91.6%	32.4%	35.3%
1989..........	19,534	18,260	18,325	5,382	93.5%	27.6%	29.4%
1990 ESTIMATE	20,380	19,193	19,193	4,633	94.2%	22.7%	24.1%
1991 ESTIMATE	20,975	19,991	20,037	5,095	95.3%	24.3%	25.4%

NOTE: In the actual years 1982-1989, the total eligible for funding includes the council recommended for approval plus unfunded carryover from the prior year. The estimates for 1990 and 1991 do not include anticipated carryover except for DRR.

DHHS-Nati tutes of Health
ARY
Distribution by Mechanism

(Dollars in Thousands)

Mechanism	1982 Amount	1982 Percent To Total	1983 Amount	1983 Percent To Total	1984 Amount	1984 Percent To Total	1985 Amount	1985 Percent To Total	1986 Amount	1986 Percent To Total
Research Project Grants	$1,832,867	50.3	$2,095,116	52.2	$2,389,553	53.2	$2,769,899	54.1	2,922,221	55.1
Research Centers.......	349,091	9.6	373,369	9.3	428,373	9.5	475,968	9.3	474,254	8.9
Other Research.........	208,260	5.7	217,953	5.4	243,309	5.4	308,993	6.0	304,186	5.7
Total, Res. Grants...	2,390,218	65.6	2,686,438	66.9	3,061,235	68.1	3,554,860	69.4	3,700,661	69.8
Research Training......	150,474	4.1	164,654	4.1	166,462	3.7	217,467	4.2	212,780	4.0
R & D Contracts........	320,531	8.8	320,090	8.0	344,642	7.7	375,176	7.3	398,009	7.5
Intramural Research....	451,730	12.4	498,210	12.4	539,514	12.0	571,595	11.2	580,421	11.0
Res. Mgt. & Support....	187,443	5.1	200,937	5.0	213,026	4.7	219,310	4.3	214,640	4.0
All Other 1/...........	143,065	3.9	142,806	3.6	168,674	3.8	183,149	3.6	193,907	3.7
Total, NIH........	3,643,461	100.0	4,013,135	100.0	4,493,553	100.0	5,121,557	100.0	5,300,418	100.0

Mechanism	1987 2/ Amount	1987 2/ Percent To Total	1988 3/ Amount	1988 3/ Percent To Total	1989 4/ Amount	1989 4/ Percent To Total	1990 Estimate 5/ Amount	1990 Estimate 5/ Percent To Total	1991 Estimate Amount	1991 Estimate Percent To Total
Research Project Grants	3,463,578	56.1	3,739,855	56.6	4,033,421	56.3	4,197,957	55.4	4,424,775	55.8
Research Centers.......	524,690	8.5	563,800	8.5	605,107	8.5	634,938	8.4	669,626	8.4
Other Research.........	351,450	5.7	371,374	5.6	370,936	5.2	378,738	5.0	357,709	4.5
Total, Res. Grants...	4,339,718	70.3	4,675,029	70.7	5,009,464	70.0	5,211,633	68.8	5,452,110	68.8
Research Training......	232,725	3.8	238,954	3.6	255,558	3.6	286,662	3.8	291,623	3.7
R & D Contracts........	481,867	7.8	496,993	7.5	543,184	7.6	576,495	7.6	592,909	7.5
Intramural Research....	665,311	10.8	715,039	10.8	788,318	11.0	855,947	11.3	914,913	11.5
Res. Mgt. & Support....	239,082	3.9	271,447	4.1	302,110	4.2	317,713	4.2	339,702	4.3
All Other 1/...........	216,335	3.5	212,968	3.2	259,344	3.6	327,902	4.3	338,429	4.3
Total, NIH........	6,175,038	100.0	6,610,430	100.0	7,157,978	100.0	7,576,352	100.0	7,929,686	100.0

NOTE: Data for FY 1982-1989 reflects actual obligations.

1/ Includes Cancer Control, Construction, National Library of Medicine, Office of the Director, and Buildings and Facilities.
2/ Includes $5,050 in research project grants as reimbursements from the Office of the Director.
3/ Includes $5,159 in research project grants as reimbursements from the Office of the Director.
4/ Includes carryover funds for construction obligated in 1989 in DRR, NLM & B&F in the amount of $35,112.
5/ Reflects administrative reductions of $24,428 and sequestration in the amount of $96,590.
Includes $15,000 for extramural construction provided for in P.L. 101-166.

DHHS-National I[illegible]s of Health

HISTORY OF CONGRESSIONAL APPROPRIATIONS, 1981-1991 ESTIMATE

INCLUDES AIDS

	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990 Estimate	1991 Estimate
NCI...............	27.7%	27.1%	24.5%	24.1%	23.0%	22.9%	22.7%	22.0%	22.0%	21.6%	21.4%
NHLBI.............	15.4%	15.4%	15.5%	15.7%	15.6%	15.6%	15.0%	14.5%	14.6%	14.2%	14.0%
NIDR..............	2.0%	2.0%	2.0%	2.0%	2.0%	1.9%	1.9%	1.9%	1.8%	1.8%	1.8%
NIADDK............	10.4%	10.1%	10.3%	10.3%	10.6%	10.4%	8.3%	8.0%	7.8%	7.7%	7.6%
NINCDS............	7.1%	7.3%	7.4%	7.5%	7.7%	7.9%	7.9%	8.0%	6.6%	6.5%	6.5%
NIAID.............	6.5%	6.5%	6.9%	7.1%	7.2%	7.0%	8.8%	9.6%	10.4%	11.0%	11.2%
NIGMS.............	9.4%	9.3%	9.2%	9.3%	9.4%	9.4%	9.2%	9.6%	9.6%	9.4%	9.4%
NICHD.............	6.2%	6.2%	6.3%	6.1%	6.1%	5.9%	5.9%	6.0%	6.0%	5.8%	5.8%
NEI...............	3.3%	3.5%	3.5%	3.5%	3.5%	3.5%	3.5%	3.4%	3.2%	3.1%	3.1%
NIEHS.............	2.6%	2.9%	4.1%	4.0%	3.8%	3.6%	3.4%	3.2%	3.1%	3.0%	3.0%
NIA...............	2.1%	2.2%	2.3%	2.6%	2.8%	2.8%	2.9%	2.9%	3.1%	3.2%	3.1%
NIAMS.............	---	---	---	---	---	---	2.2%	2.2%	2.2%	2.2%	2.2%
NIDCD.............	---	---	---	---	---	---	---	---	1.3%	1.6%	1.5%
DRR...............	4.9%	5.1%	5.3%	5.4%	5.9%	5.6%	5.2%	5.5%	4.8%	4.4%	4.0%
NCNR..............	---	---	---	---	---	---	0.3%	0.4%	0.4%	0.4%	0.4%
NCHR..............	---	---	---	---	---	---	0.0%	0.0%	0.4%	0.8%	1.4%
FIC...............	0.3%	0.3%	0.3%	0.3%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%
Subtotal, IRD's...	97.8%	97.8%	97.7%	97.7%	97.7%	96.5%	97.6%	97.4%	97.7%	96.9%	96.7%
NLM...............	1.3%	1.2%	1.3%	1.1%	1.1%	1.1%	1.0%	1.0%	1.1%	1.1%	1.1%
OD................	0.6%	0.6%	0.6%	0.6%	0.7%	2.1%	0.9%	0.8%	0.7%	1.2%	1.0%
B & F.............	0.3%	0.3%	0.4%	0.6%	0.4%	0.3%	0.5%	0.7%	0.5%	0.8%	1.1%
TOTAL, NIH........	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

* Less than .1 percent.

DHHS-Nat. ..stitutes of Health

HISTORY OF CONGRESSIONAL APPROPRIATIONS, 1981-1991 ESTIMATE

EXCLUDES AIDS

	1981	1/ 1982	2/ 1983	1984	1985	3/ 1986	4/ 1987	5/ 1988	1989	1990 Estimate	1991 Estimate
NCI................	27.7%	27.0%	24.4%	23.9%	22.7%	22.6%	22.6%	22.3%	22.1%	21.7%	21.5%
NHLBI..............	15.4%	15.4%	15.6%	15.7%	15.7%	15.7%	15.4%	15.2%	15.4%	15.1%	15.0%
NIDR...............	2.0%	2.0%	2.0%	2.0%	2.0%	1.9%	1.9%	2.0%	1.9%	1.9%	1.9%
NIADDK.............	10.4%	10.1%	10.3%	10.4%	10.7%	10.6%	8.6%	8.6%	8.5%	8.4%	8.4%
NINCDS.............	7.1%	7.3%	7.4%	7.5%	7.8%	8.1%	8.2%	7.2%	7.0%	6.9%	6.9%
NIAID..............	6.5%	6.5%	6.7%	6.7%	6.8%	6.0%	6.7%	6.7%	6.6%	6.4%	6.5%
NIGMS..............	9.4%	9.3%	9.2%	9.3%	9.5%	9.6%	9.5%	10.2%	10.3%	10.2%	10.2%
NICHD..............	6.2%	6.2%	6.4%	6.2%	6.2%	6.0%	6.1%	6.1%	6.2%	6.1%	6.1%
NEI................	3.3%	3.5%	3.5%	3.5%	3.6%	3.6%	3.7%	3.6%	3.5%	3.4%	3.4%
NIEHS..............	2.6%	2.9%	4.1%	4.1%	3.8%	3.7%	3.5%	3.4%	3.4%	3.3%	3.2%
NIA................	2.1%	2.3%	2.3%	2.6%	2.8%	2.9%	3.0%	3.1%	3.4%	3.5%	3.5%
NIAMS..............	---	---	---	---	---	---	2.3%	2.4%	2.4%	2.5%	2.4%
NIDCD..............	---	---	---	---	---	---	---	1.2%	1.4%	1.7%	1.7%
DRR................	4.9%	5.0%	5.3%	5.4%	5.9%	5.6%	5.3%	5.1%	4.5%	4.3%	3.8%
NCNR...............	---	---	---	---	---	---	0.3%	0.4%	0.4%	0.5%	0.5%
NCHGR..............	---	---	---	---	---	---	---	---	0.4%	0.9%	1.5%
FIC................	0.3%	0.3%	0.3%	0.3%	0.2%	0.2%	0.2%	0.2%	0.1%	0.2%	0.2%
Subtotal, IRD's...	97.8%	97.8%	97.6%	97.7%	97.7%	96.5%	97.5%	97.6%	97.7%	96.9%	96.8%
NLM................	1.3%	1.2%	1.3%	1.1%	1.1%	1.1%	1.0%	1.1%	1.2%	1.2%	1.3%
OD.................	0.6%	0.6%	0.6%	0.6%	0.8%	2.2%	1.0%	0.8%	0.6%	1.2%	1.0%
B & F..............	0.3%	0.3%	0.4%	0.6%	0.4%	0.3%	0.5%	0.5%	0.5%	0.7%	1.0%
TOTAL, NIH........	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Research Projects Grants
Adjustments From Full Cost

Competing Research Project Grants

	FY 1989	FY 1990	FY 1991
NCI..............	-13.5	-10.2	-20.0
NHLBI............	-11.5	-13.9	-13.9
NIDR.............	-10.6	-15.0	-15.0
NIDDK............	-10.5	-12.0	-10.9
NINDS............	-10.6	-17.4	-25.1
NIAID............	-10.0	-12.0	-10.0
NIGMS............	-10.6	-12.4	-12.7
NICHD............	-14.0	-12.0	-12.0
NEI..............	-10.0	-11.0	-10.3
NIEHS............	-11.8	-9.7	-7.3
NIA..............	-10.0	-15.4	-10.4
NAIMS............	-12.0	-12.2	-11.5
NIDCD............	-10.0	-10.6	-8.0
DRR..............	---	-10.1	---
NCNR.............	-10.0	-12.3	-16.5
NCHGR............	---	-9.5	-10.4
NIH AVERAGE	-11.4	-12.5	-14.4

Noncompeting Research Projects Grants

	FY 1989	FY 1990	FY 1991
NCI..............	-1.6	-4.7	-4.0
NHLBI............	-13.3	-14.5	-11.0
NIDR.............	-13.7	-12.0	-12.0
NIDDK............	-10.5	-12.0	-10.9
NINDS............	-8.0	-11.1	-12.0
NIAID............	-12.0	-12.0	-10.0
NIGMS............	-10.2	-11.2	-12.7
NICHD............	-10.8	-15.0	-15.5
NEI..............	-8.8	-11.0	-10.3
NIEHS............	-8.3	-8.3	-5.0
NIA..............	-12.5	-13.0	-10.5
NIAMS............	-11.9	-12.0	-11.8
NIDCD............	-10.0	-9.3	-9.0
DRR..............	---	---	-10.1
NCNR.............	1.1	-11.8	-17.8
NCHGR............	---	-4.8	-5.0
NIH AVERAGE	-9.5	-11.1	-10.1

03/05/90

NISTOT

NATIONAL INSTITUTES OF HEALTH
FULL TIME EQUIVALENT POSITIONS

	FY 81	FY 82	FY 83	FY 84	FY 85	FY 86	FY 87	FY 88	FY 89	FY 90 ESTIMATE	FY 91 REQUEST
NCI											
IR	1,626	1,615	1,760	1,769	1,645	1,557	1,556	1,683	1,613	1,682	1,721
RMS	449	446	477	522	456	415	424	453	422	432	432
CC	65	65	80	125	129	129	130	147	138	148	155
SUBTOTAL	2,140	2,126	2,317	2,416	2,230	2,101	2,110	2,283	2,173	2,262	2,308
NHLBI											
IR	411	409	438	431	409	395	400	418	412	412	424
RMS	425	421	435	432	438	411	433	447	430	422	431
SUBTOTAL	836	830	873	863	847	806	833	865	842	834	855
NIDR											
IR	219	217	233	267	253	252	263	274	262	263	270
RMS	130	131	119	68	75	77	74	70	73	78	84
SUBTOTAL	349	348	352	335	328	329	337	344	335	341	354
NIDDK 1/											
IR	488	472	493	519	490	417	433	446	435	428	439
RMS	180	184	186	197	184	165	162	164	162	175	179
SUBTOTAL	668	656	679	716	674	582	595	610	597	603	618
NINDS 2/											
IR	410	426	454	467	457	453	488	494	468	478	481
RMS	231	239	235	227	209	205	200	199	184	187	187
SUBTOTAL	641	665	689	694	666	658	688	693	652	665	668
NIAID											
IR	502	497	527	558	556	517	525	557	573	656	711
RMS	176	169	178	187	181	185	207	249	297	377	405
SUBTOTAL	678	666	705	745	737	702	732	806	870	1,033	1,116
NIGMS											
IR	22	22	20	22	22	20	18	17	18	22	22
RMS	139	144	147	147	139	137	138	136	140	151	154
SUBTOTAL	161	166	167	169	161	157	156	153	158	173	176
NICHD											
IR	218	226	258	265	254	256	262	242	263	261	264
RMS	195	195	197	197	179	165	166	195	175	173	176
SUBTOTAL	413	421	455	462	433	421	428	437	438	434	440
NEI											
IR	111	122	159	163	151	137	138	156	152	156	161
RMS	74	80	68	71	64	61	58	61	60	68	68
SUBTOTAL	165	202	227	234	215	198	196	217	212	224	229
NIEHS											
IR	454	485	594	608	587	568	603	605	581	586	594
RMS	85	85	74	87	83	77	79	84	86	87	69
SUBTOTAL	539	570	668	695	670	665	682	689	667	673	683

HISTOT

03/05/90

NATIONAL INSTITUTES OF HEALTH
FULL TIME EQUIVALENT POSITIONS

	FY 81	FY 82	FY 83	FY 84	FY 85	FY 86	FY 87	FY 88	FY 89	FY 90 ESTIMATE	FY 91 REQUEST
NIA											
IR	234	243	264	266	253	242	247	250	244	243	250
RMS	105	108	112	112	103	99	99	106	112	126	131
SUBTOTAL	339	351	376	378	356	341	346	356	356	369	381
NIAMS											
IR	0	0	0	0	0	36	39	47	53	57	61
RMS	0	0	0	0	0	13	28	57	60	59	61
SUBTOTAL	0	0	0	0	0	49	67	104	113	116	122
NIDCD											
IR	0	0	0	0	0	0	0	0	20	24	28
RMS	0	0	0	0	0	0	0	0	17	38	42
SUBTOTAL	0	0	0	0	0	0	0	0	37	62	70
DRR											
RMS	90	92	96	91	91	86	89	97	94	89	90
SUBTOTAL	90	92	96	91	91	86	89	97	94	89	90
NCNR											
IR	0	0	0	0	0	0	0	0	0	0	2
RMS	0	0	0	0	0	5	15	26	31	30	35
SUBTOTAL	0	0	0	0	0	5	15	26	31	30	37
3/											
[illegible]	0	0	0	0	0	0	0	0	0	30	38
SUBTOTAL	0	0	0	0	0	0	0	0	0	30	38
FIC											
RMS	49	54	55	61	60	56	56	58	58	64	67
SUBTOTAL	49	54	55	61	60	56	56	58	58	64	67
SUBTOTAL, ICDs											
IR	4,695	4,734	5,200	5,335	5,077	4,870	4,972	5,189	5,094	5,268	5,420
RMS	2,328	2,348	2,379	2,399	2,262	2,157	2,228	2,402	2,401	2,586	2,669
CC	65	65	80	125	129	129	130	147	138	148	155
SUBTOTAL, IRDs	7,088	7,147	7,659	7,859	7,468	7,156	7,330	7,738	7,633	8,002	8,252
NLM	521	519	526	544	531	501	510	510	511	524	537
OD	582	595	591	587	567	506	504	514	558	601	612
CENTRAL SERVICES	4,446	4,428	4,638	4,671	4,534	4,377	4,376	4,487	4,502	4,652	4,732
TOTAL, NIH	12,637	12,689	13,414	13,661	13,100	12,540	12,720	13,249	13,204	13,779	14,133

1/ Prior to FY 1986, FTEs included both NIDDK and NIAMS.
2/ Prior to FY 1989, FTEs included both NINDS and NIDCD.
3/ Prior to FY 1990, FTEs included in OD.

IR = Intramural Research
RMS = Research Management and Support
CC = Cancer Control

Research Projects Grants
Adjustments From Full Cost
(Exclusive of Adjustments for unobligated balances)

Competing Research Project Grants

	FY 1989	FY 1990	FY 1991
NCI..............	-13.5	-10.2	-20.0
NHLBI............	-11.5	-13.9	-13.9
NIDR.............	-10.6	-15.0	-15.0
NIDDK............	-10.5	-12.0	-10.9
NINDS............	-10.6	-17.4	-25.1
NIAID............	-10.0	-12.0	-10.0
NIGMS............	-10.6	-12.4	-12.7
NICHD............	-14.0	-12.0	-12.0
NEI..............	-10.0	-11.0	-10.3
NIEHS............	-11.8	-9.7	-7.3
NIA..............	-10.0	-15.4	-10.4
NAIMS............	-12.0	-12.2	-11.5
NIDCD............	-10.0	-10.6	-8.0
DRR..............	---	-10.1	---
NCNR.............	-10.0	-12.3	-16.5
NCHGR............	---	-9.5	-10.4
NIH AVERAGE	-11.4	-12.5	-14.4

Noncompeting Research Projects Grants

	FY 1989	FY 1990	FY 1991
NCI..............	-1.6	-4.7	-4.0
NHLBI............	-13.3	-14.5	-11.0
NIDR.............	-13.7	-12.0	-12.0
NIDDK............	-10.5	-12.0	-10.9
NINDS............	-8.0	-11.1	-12.0
NIAID............	-12.0	-12.0	-10.0
NIGMS............	-10.2	-11.2	-12.7
NICHD............	-10.8	-15.0	-15.5
NEI..............	-8.8	-11.0	-10.3
NIEHS............	-8.3	-8.3	-5.0
NIA..............	-12.5	-13.0	-10.5
NIAMS............	-11.9	-12.0	-11.8
NIDCD............	-10.0	-9.3	-9.0
DRR..............	---	---	-10.1
NCNR.............	1.1	-11.8	-17.8
NCHGR............	---	-4.8	-5.0
NIH AVERAGE	-9.5	-11.1	-10.1

NATIONAL INSTITUTES OF HEALTH
FULL TIME EQUIVALENT POSITIONS

	FY 81	FY 82	FY 83	FY 84	FY 85	FY 86	FY 87	FY 88	FY 89	FY 90 ESTIMATE	FY 91 REQUEST
NCI											
IR	1,626	1,615	1,760	1,769	1,645	1,557	1,556	1,683	1,613	1,682	1,721
RMS	449	446	477	522	456	415	424	453	422	432	432
CC	65	65	80	125	129	129	130	147	138	148	155
SUBTOTAL	2,140	2,126	2,317	2,416	2,230	2,101	2,110	2,283	2,173	2,262	2,308
NHLBI											
IR	411	409	438	431	409	395	400	418	412	412	424
RMS	425	421	435	432	438	411	433	447	430	422	431
SUBTOTAL	836	830	873	863	847	806	833	865	842	834	855
NIDR											
IR	219	217	233	267	253	252	263	274	262	263	270
RMS	130	131	119	68	75	77	74	70	73	78	84
SUBTOTAL	349	348	352	335	328	329	337	344	335	341	354
NIDDK 1/											
IR	488	472	493	519	490	417	433	446	435	428	439
RMS	180	184	186	197	184	165	162	164	162	175	179
SUBTOTAL	668	656	679	716	674	582	595	610	597	603	618
NINDS 2/											
IR	410	426	454	467	457	453	488	494	468	478	481
RMS	231	239	235	227	209	205	200	199	184	187	187
SUBTOTAL	641	665	689	694	666	658	688	693	652	665	668
NIAID											
IR	502	497	527	558	556	517	525	557	573	656	711
RMS	176	169	178	187	181	185	207	249	297	377	405
SUBTOTAL	678	666	705	745	737	702	732	806	870	1,033	1,116
NIGMS											
IR	22	22	20	22	22	20	18	17	18	22	22
RMS	139	144	147	147	139	137	138	136	140	151	154
SUBTOTAL	161	166	167	169	161	157	156	153	158	173	176
NICHD											
IR	218	226	258	265	254	256	262	242	263	261	264
RMS	195	195	197	197	179	165	166	195	175	173	176
SUBTOTAL	413	421	455	462	433	421	428	437	438	434	440
NEI											
IR	111	122	159	163	151	137	138	156	152	156	161
RMS	74	80	68	71	64	61	58	61	60	68	68
SUBTOTAL	185	202	227	234	215	198	196	217	212	224	229
NIEHS											
IR	454	485	594	608	587	588	603	605	581	586	594
RMS	85	85	74	87	83	77	79	84	86	87	89
SUBTOTAL	539	570	668	695	670	665	682	689	667	673	683

HISTOT

03/05/90

NATIONAL INSTITUTES OF HEALTH
FULL TIME EQUIVALENT POSITIONS

	FY 81	FY 82	FY 83	FY 84	FY 85	FY 86	FY 87	FY 88	FY 89	FY 90 ESTIMATE	FY 91 REQUEST
NIA											
IR	234	243	264	266	253	242	247	250	244	243	250
RMS	105	108	112	112	103	99	99	106	112	126	131
SUBTOTAL	339	351	376	378	356	341	346	356	356	369	381
NIAMS											
IR	0	0	0	0	0	36	39	47	53	57	61
RMS	0	0	0	0	0	13	28	57	60	59	61
SUBTOTAL	0	0	0	0	0	49	67	104	113	116	122
NIDCD											
IR	0	0	0	0	0	0	0	0	20	24	28
RMS	0	0	0	0	0	0	0	0	17	38	42
SUBTOTAL	0	0	0	0	0	0	0	0	37	62	70
DRR											
RMS	90	92	96	91	91	86	89	97	94	89	90
SUBTOTAL	90	92	96	91	91	86	89	97	94	89	90
NCNR											
IR	0	0	0	0	0	0	0	0	0	0	2
RMS	0	0	0	0	0	5	15	26	31	30	35
SUBTOTAL	0	0	0	0	0	5	15	26	31	30	37
NCHGR 3/											
RMS	0	0	0	0	0	0	0	0	0	30	38
SUBTOTAL	0	0	0	0	0	0	0	0	0	30	38
FIC											
RMS	49	54	55	61	60	56	56	58	58	64	67
SUBTOTAL	49	54	55	61	60	56	56	58	58	64	67
SUBTOTAL, ICDs											
IR	4,695	4,734	5,200	5,335	5,077	4,870	4,972	5,189	5,094	5,268	5,428
RMS	2,328	2,348	2,379	2,399	2,262	2,157	2,228	2,402	2,401	2,586	2,669
CC	65	65	80	125	129	129	130	147	138	148	155
SUBTOTAL, IRDs	7,088	7,147	7,659	7,859	7,468	7,156	7,330	7,738	7,633	8,002	8,252
NLM	521	519	526	544	531	501	510	510	511	524	537
OD	582	595	591	587	567	506	504	514	558	601	612
CENTRAL SERVICES	4,446	4,428	4,638	4,671	4,534	4,377	4,376	4,487	4,502	4,652	4,732
TOTAL, NIH	12,637	12,689	13,414	13,661	13,100	12,540	12,720	13,249	13,204	13,779	14,133

1/ Prior to FY 1986, FTEs included both NIDDK and NIAMS.
2/ Prior to FY 1989, FTEs included both NINDS and NIDCD.
3/ Prior to FY 1990, FTEs included in OD.

IR = Intramural Research
RMS = Research Management and Support
CC = Cancer Control

Mr. Natcher. Dr. Raub, if you will review for the committee briefly the overall funding for NIH over the last ten years and tell us what this has meant in terms of the number of grants, centers, and trainees?

Dr. Raub. There are several highlights for those tables. First is the growth in the ten year period from $3.6 billion to $7.9 billion, approximately a doubling in the investment in current dollars, and a 36 percent increase in buying power when that number is adjusted for inflation.

Perhaps the most dramatic change is the growth of expenditures on AIDS research from a little over $3,000,000 in 1982 to the $800,000,000 requested for fiscal year 1991.

The research project grant category accounted for the largest growth not only in absolute terms but also in relative terms, going from 50 percent of our expenditures in 1982 to 56 percent in our current budget proposal. The total number of grants has grown from just under 16,000 in 1982 to a high of 20,681 in 1989. The total number of competing grants has fluctuated from the high point in 1987 of 6,453, to a low in FY 1990 of 4,633.

Along the way, there has been modest, steady growth in the centers and training efforts with emphasis on biotechnology and the genome.

PEACE DIVIDEND

Mr. Natcher. I mentioned a few minutes ago that it was called to the attention of the three gentlemen in our committee that during the last nine years, $2,312,000,000 has been appropriated by the Congress and spent by the Department of Defense. During that period, we had approximately 48,000,000,000 for NIH. We are all amazed about what is happening abroad. We don't know fully what will happen in the end but I have said to many, any part they cut out of defense ought to come to health and education. That is where we ought to spend the money. I don't know if they are listening. We will find out in a few months. That is where it ought to go, health and education.

LENGTH OF GRANTS

The small number of new grants in 1990, has caused great concern. At least part of the reason for this is NIH's decision several years ago to extend the average length of each grant. What can you tell us at this time about the extent of this change and the impact on the 1990 budget for grants?

Dr. Raub. I think your observation is correct, Mr. Chairman, increasing the average length of awards is a contributor to that phenomenon, but only one of several forces. The largest contribution comes from the fact that during the middle years of the 1980s for four years in succession, the number of competing research project grants was more than 6,000. It is the future year commitments of those that are the biggest contribution to the commitment base.

Mr. Natcher. Thank you, Dr. Raub.

Mr. Pursell, I yield to you.

INFANT MORTALITY

Mr. **Pursell**. Thank you very much.

We appreciate your leadership, Dr. Raub.

Infant mortality, what are any of the institutes doing with respect to that subject? That seems to be a national priority. Infant mortality rates are extremely high in urban areas and black communities and the like. Tell us what priorities you might have for this year and where you see that problem going nationally. We really don't have any components in Health and Human Services with respect to infant mortality. Counties, cities, states are looking at commissions and trying to figure out how to solve that problem. Where are we in the research components of that?

Dr. **Raub**. For NIH, our focus is on addressing research problems whose answers might facilitate either the prevention of the low birth weight infant, or maximize the likelihood that a low birth weight or premature infant would be able to survive. Overall, this year, we expect to spend on the order of $130 million in that respect and are projecting somewhat over $140 million next year.

That involves the programs of about ten institutes. The flagship is the National Institute of Child Health and Human Development. It has a major series of research efforts ranging from basic science to several networks of clinical trial activities, some focused on prevention of low birth weight by doing research on everything from teenage pregnancy to facilitating access to better care and better general knowledge for pregnant women. Another network of clinical trials involves high tech care for premature infants. We plan to continue strong efforts in all those areas with special emphasis on further outreach into the minority population, who bear a disproportionate part of that burden.

Mr. **Pursell**. One of the problems we are finding is that there is a shortage of doctors and that malpractice is keeping OBs from wanting to practice in urban areas, and unwillingness to serve that infant mortality problem. It is not one of research, it is one of basic economics. The threat of malpractice and the threat of malpractice legislation. I know that is not your field, but maybe it should be.

Dr. **Raub**. I think we have more ideas about the research part of the agenda.

DISEASE PREVENTION

Mr. **Pursell**. How about the whole thrust nationally of good nutrition mixed with a good dose of exercise, similar to programs like Pritiken and others, that have been demonstrated to be extremely effective in the long term in efforts to keep people healthy?

Dr. **Raub**. We are addressing that public recognition, reasserting the basics about exercise, nutrition and other healthy lifestyles.

The National Institutes of Health has been the focus of nutrition research with animals and humans for many years. We have continued to do the kinds of basic studies and clinical studies that we think advance that knowledge. In recent years, we have been increasingly funding research on lifestyles as components of fighting some diseases like cancer and heart disease. As you see those programs evolve, you will continue to see lifestyle components emerging as important research leads and parts of programs designed to prevent those disorders.

Mr. **Pursell.** I see no major components in HHS with respect to a policy driving a health education program that includes those two as an integral part of our health program for the country. It seems like the country is ahead of the government basically in this area.

Dr. **Raub.** The approach that the Department and NIH have taken over the years is to avoid pulling nutritional activities into a single organizational focus. It is important that they do not get uncoupled from the scientific and clinical programs. Our approach has been rather to create the coordination structures that we think give us the best of both worlds, structures that have strong roots in the clinical sciences and, at the same time, have a coherent, overall program.

NIH has a unit based in the Office of the Director, whose sole purpose is the coordination of nutrition research activities. That unit is coupled with a component in the Office of the Assistant Secretary of Health and components within the U.S. Department of Agriculture.

AIDS

Mr. **Pursell.** The AIDS subject has bothered me for some time. We are up to $1,600,000,000, somewhere in that figure. I realize some of the AIDS research has implications to other aspects of disease efforts, but right now, funding-wise, it is beginning to surpass all the other institutes in terms of funding. Where do you see that leveling out or coming to some degree of reasonable balance? So we don't get more deaths and chronic illnesses than we do with AIDS, we are pushing this program. I think it will level off somewhere, but where do you see that down the road?

Dr. **Raub.** The developments in AIDS have come so rapidly and some with such surprise that none of us are in a good position to speculate much beyond the coming year. The proposal for a $800,000,000 level for next year presents a slight slowing of the growth rate compared to earlier years, but still a substantial investment. We think this is commensurate not only with the scope of the immediate problem but also with the number and quality of research leads that exist.

As you said, there are the many secondary benefits that will occur from a deeper understanding of viruses and the immune system. We believe the projected level of investment is well placed. We think it will reap dividends far beyond the AIDS efforts.

NATIONAL CENTER FOR NURSING RESEARCH

Mr. **Pursell.** Aside from OMB, would you object if we added additional funding for the National Center for Nursing Research, since this is the bottom end of funding? We are at $33,000,000. The next one below that is DRR and NIDCD is $122 million going up the ladder. We are really getting a lot of requests for grants and just are unable to fund those because of the limited amount of dollars.

Dr. Raub. The numbers, as you report, are in fact a manifestation of success.

Mr. Pursell. Success at what, politics?

Dr. Raub. No. As the Center has developed, it has proved to be a very strong magnet for interest in nursing research. So we are seeing more applications than we might have predicted. Also, we are seeing more applications in the areas that are clinically oriented, as opposed to an orientation of behavioral sciences. The applications with the clinical orientation tend to be more labor intensive and have higher concentrations of cost. We believe in the ability of the National Center for Nursing Research to mobilize interest and talent.

Mr. Pursell. When you look at the other institutes, it is at the bottom of the totem pole. I know you can't do anything about that particularly. Do they get any AIDS research money?

Dr. Raub. Yes. There is some AIDS research money, approximately $1.1 million in our 1991 request.

Mr. Pursell. I think my time has expired. Thank you.

Mr. Natcher. Mr. Stokes.

BUDGET REDUCTIONS

Mr. Stokes. Thank you, Mr. Chairman.

Dr. Raub, your Fiscal Year 1990 budget was about $7.6 billion for NIH. Then you had to take about a $24 million hit, and then sequestration reduced you budget by another $96.6 million. How have these cuts been distributed across NIH programs? That is for grants, contracts, and so forth? I am particularly interested in how these cuts affected the number of competing research grants since the number of competing research grants expected to be funded in fiscal year 1990 is 4,633, far below the number funded in fiscal year 1989, which was 5,382.

Dr. Raub. Each of the cuts had their own character, so they impacted different parts of the budget. For example, the reduction in monies as a result of the cap on extramural salaries impacted the personnel cost category in research project grants, but did not otherwise change the numbers of the grants.

The reduction for salaries and expenses came against the agency's salary and expense lines. The reduction for procurement came primarily against our intramural program's operating costs.

The largest single reduction, $96.6 million, was the result of sequestration. The reduction was applied, as the rules called for, against each activity. For research project grants, instead of funding about 4,755 research project grant applications in the competing group, we could fund only 4,633. A little over 100 project grants were cut.

EXTRAMURAL PAY CAP

Mr. Stokes. How is the limit on investigator salaries of $120,000 working? Are you finding that colleges and universities are adding to this amount?

Dr. Raub. As best we can tell from our perspective, it is moving forward without particular difficulty. The $10 million estimate seems to be about right in terms of the savings. To the extent that institutional salary levels exceed that, to the best of our knowledge, the institutions are meeting the difference by other sources of funds available to them. We are not aware of any particular problems, and certainly no crises, as a result of it.

CONFLICT OF INTEREST

Mr. STOKES. Dr. Raub, what is the status of your conflict of interest guidelines?

Dr. RAUB. As you probably know from news reports, the draft set of guidelines that we published for comment received over 700 responses. On the basis of those responses, the Department determined that considerable additional analysis and planning was needed before we would proceed in any attempt at rule-making.

We are now in the process not only of digesting all those comments, but also of attempting to reformulate the issues as a way of assuring that NIH recognizes very well that there is a critical interdependence between the academic community and industry specifically the biotechnology industry. NIH, having been the single principal source whose funding led to the creation of the industry, does not want to be the institution that makes the industry founder.

I expect that over the coming months we will be making public, some recast ideas that will focus on particular parts of the conflict of interest issues. We are confident that we can do that in cooperation with the venture capital industry and biotechnology industries. We are also confident that we can address the few problems that are real and not even suggest that we are somehow erecting a structure that is much more complicated than necessary.

HUMAN GENOME

Mr. STOKES. I have recently received several letters from investigators at institutions in my district who believe it unwise to support human genome research at the current level of $60,000,000. They said they believe too much money is being put into this program at the present time.

The request for fiscal year 1991 is an 81.5 percent increase, $48.5 million. Given the other competing research priorities, what is the justification for this increase?

Dr. RAUB. The principal justification is the extraordinary promise that the genome project presents not only in long-term benefits, but also in short-term benefits. In the long-term, we will have in hand the complete description of us and the many benefits, many of them not now predictable, that would redound in terms of understanding disease and being able to intervene and even prevent it. And in the short-term, with our emphasis on developing powerful tools, we believe there will be immediate benefits to the rest of the biomedical sciences as new tools emerge for handling the genetic material, as well as dealing with the computer systems in which that information resides.

While we think there are difficult trade-offs between exploring the genome and other opportunities, we believe it deserves to be one of our highest priority investments.

Mr. STOKES. To what degree are minority investors participating in the human genome research?

Dr. RAUB. One of the topics of discussion underway in the National Center for Human Genome Research and the historically black and minority institutions is just that. Investigators in those institutions with an interest in molecular biology and its applications might become part of the human genome effort. We will be addressing that seriously over the coming months.

Mr. STOKES. Currently are any minorities represented on the Human Genome Advisory Committee?

Dr. RAUB. That is one I would have to supply for the record.

DRR REORGANIZATION

Mr. STOKES. When you were here last year you were in the process of reorganizing the Division of Research Resources, which is the home of several minority programs—MBRS, RCMI, MHSSAP. What is the current status of this reorganization?

Dr. RAUB. The reorganization has been completed, with approval last month by Secretary Sullivan of the reorganization package. The programs are operating in their respective places and we believe, well.

MINORITY PROGRAMS

Mr. STOKES. How close are you to filling the position of Director of Minority Programs?

Dr. RAUB. We are in the final stages of negotiation. There are some details to be worked out over salary and other issues, but we have the approval of the Secretary in terms of our approach. We are hopeful that we can complete the details soon.

Mr. STOKES. Dr. Raub, what is the total funding at NIH for programs targeted toward minority researchers?

Dr. RAUB. In the current fiscal year, the several programs that are the heart of our investments toward minority individuals or minority institutions, total just over $70,000,000. There are also additional funds that are part of the research programs of the institutes, for example, summer programs.

For the four major minority programs, we are projecting a major increase for a total of almost $90,000,000 in fiscal year 1991.

Mr. STOKES. Can you tell me what percentage of the total NIH budget these figures represent?

Dr. RAUB. The figures I gave you are just under one percent of the budget in fiscal year 1990 and would be just over one percent of the budget in fiscal year 1991.

Mr. STOKES. Can you review for me the increases in the fiscal year 1991 budget for programs that are targeted toward minorities?

Dr. RAUB. Yes sir. I will focus on the four major ones. You are familiar with the Research Centers in Minority Institutions. That program will increase from $19.5 million this year to $24.7 million next year.

The Minority Biomedical Research Support Program is increasing from $39.6 million to $43.3 million.

The Minority Access to Research Careers Program is increasing from $10.7 to $13.4. This program is part of the training effort.

As part of the reorganization, the MBRS and the MARC programs, while maintaining their individual identities, are now in the same harness being managed within the National Institute of General Medical Sciences.

Last but not least, we are proposing a major increase in the Minority High School Student Apprenticeship Program from the $1.8 million in the current fiscal year to a total of $8.5 million next year, if one takes into account the request in the base program, plus the special proposal relating to the Biomedical Research Support Grant Program.

All of those activities add up to a percentage increase of about 27 percent.

Mr. STOKES. I think Dr. Watson had his hand up when you were asking about the advisory committee.

Did you want to say something?

Dr. WATSON. Yes. We have the answer to the question regarding minorities on the Human Genome Advisory Committee. Cecil Pickett from Merck in Canada is a minority and Jaime Carbonell from Carnegie Mellon is a minority. So we have two minorities on the committee. There is another minority—one woman.

Mr. STOKES. How many people are on the advisory committee?

Dr. WATSON. Twelve.

Mr. STOKES. Thank you, Dr. Watson.

Thank you, Dr. Raub.

Mr. NATCHER. Mr. Weber.

ANIMAL WELFARE

Mr. WEBER. Dr. Raub, I have a few questions about the increasingly emotional topic we are dealing with—animal rights and animal research. For the benefit of the committee, can you talk to me about the importance of animals in NIH research efforts?

Dr. RAUB. Yes sir, I will be pleased to. It is almost impossible to exaggerate the importance of animals in our research programs. Literally every major advance in medicine in the last century has been based in whole or in part on research on laboratory animals and virtually every one of our initiatives now has a dependency on animal research that is so strong that it would be literally crippled or destroyed if it were not possible to use animals in that research.

Mr. WEBER. Can you cite a few areas that you think it is legitimate to say that we would shut down a chance for a medical breakthrough?

Dr. RAUB. We were talking before about the AIDS research effort. That is as good an example as any. Despite the ability to grow and study the virus and cells in the laboratory, and despite the rapid strides of studying certain drugs in human subjects, in between those is a body of research in the laboratory with animals ranging from Chimpanzees and Rhesus monkeys on the one hand and mice and rabbits and other more traditional animals on the other.

Mr. WEBER. One of the things we hear from the animal rights advocates is that there are substitutes or alternatives. How do you respond to that?

Dr. RAUB. In general, every one of the statements that I have seen in that area has been at best a distortion, and sometimes an outright lie. To be sure, there are instances where things can be done in tissue culture that would have required an intact animal before. But, at best, they are adjuncts to animal research. In the area of testing consumer products or drugs, by using the adjuncts, one can sometimes reduce the number of animals used or simplify the testing procedure. But one cannot eliminate the use of animals for testing items available to the general public.

NIH expenditures on cell biology, tissue culture systems, and the like have been responsible for the emergence of so-called adjuncts. We will continue to invest in those as science dictates. My concern is in many instances that, however well intentioned, the encouragement for the use of so-called alternatives becomes distorted or falls upon individuals who have little understanding of science. These individuals are all too quick to believe that a computer model or something in a laboratory dish can substitute. It cannot.

Mr. WEBER. Can you say what percentage of research projects involve animals?

Dr. RAUB. Roughly on the order of 40 percent.

Mr. WEBER. Of that 40 percent, what percent are primates?

Dr. RAUB. I don't know exactly. I would say in the range of five percent or less.

USE OF ANIMALS IN AIDS RESEARCH

Mr. WEBER. I wonder if I can ask Dr. Fauci to explain a little about the role of animals on AIDS research?

Dr. FAUCI. Certainly. There are several good, concrete examples, one of which you may have heard about this past summer . There were several studies demonstrating the efficacy of a simian immunodeficiency virus vaccine in preventing infection in monkeys who were challenged by a live virus.

Science has not been able to establish whether or not protective immunity is feasible with an individual who will be challenged with HIV in a natural setting. You could not do that with a human. You would have to have an animal model. That stands out as a major example of animal research.

As Dr. Raub mentioned, in other areas such as understanding the pathogenesis of the human immunodeficiency virus, we have rodent models. The transgenic mouse model is giving us important information not only with AIDS but a number of diseases. In the severe combined immunodeficient or SCLD mouse model, in which we have reconstituted the mouse so that you have a mouse body generating a human immune system response, we have been able to demonstrate HIV infection in the mouse. This will be a major mechanism whereby we can test therapeutic agents that block the virus in animals.

There are many examples.

Mr. WEBER. I wonder if you could provide my office with an outline of use of animals in AIDS research?

Dr. FAUCI. I will be glad to.

[The information follows:]

The Use of Animals in AIDS Research

Animal models are a vital resource for studying the effects of HIV infection in a living organism. Animal research is needed for answering key issues surrounding HIV infection, such as its mechanisms of transmission, the prevention or decrease of transmission through treatment either before or immediately after exposure, and the development of therapies and vaccines to halt or curb the disease.

Studies of the early spread of the HIV virus or infection of brain tissues are most appropriately done in animals. In addition, heterosexual transmission of virus and transfer of virus and drugs from mother to newborn can now be mimicked in animal models. These models also provide the opportunity to study cofactors that may affect infection rates, such as other infections, stage of infection, frequency or number of exposures, and amount of virus present in the body.

The development of animal models of HIV infection represents a powerful tool for evaluating potential acquired immunodeficiency syndrome (AIDS) drugs and vaccines. By testing new therapies in animal models, scientists can more rationally assign priorities to drugs under preclinical development based on their efficacy and toxicity. They can also help in determining optimal doses and drug delivery schedules and reduce the burden on the clinical trials system with its inherent limits on resources. The enormous number of different combinations of drugs, doses, routes of administration, and schedules cannot all be studied in patients. Animal models provide a scientific means of selecting the most promising of these combined therapies for clinical trials. Combination chemotherapy is important for several reasons. One is the emergence of drug-resistant strains of HIV. A second issue results from the need to give AIDS patients both anti-HIV drugs and drugs to treat their opportunistic infections. At present, one therapy must often be stopped to begin another. Further studies are needed to develop the potential to continue anti-HIV therapy in combination with therapies for opportunistic infections.

Animal models are currently being used to screen new drugs for efficacy against three opportunistic infectious agents associated with AIDS: *Pneumocystis carinii*, *Mycobacterium avium*, and *Candida albicans*. The models also provide the opportunity to study the causes of these infections and their deleterious effects on the body.

NIAID sponsors research in drug development using murine (mouse), feline (cat), and simian (monkey) animal models of retroviral infections. An especially important model for HIV infection is the simian immunodeficiency virus (SIV) disease model in macaques. Genetically similar to HIV, SIV infection results in a progressive disease that resembles AIDS. Another model, the severe combined immunodeficiency (SCID) mouse, is being developed with the assistance of NIAID staff. Mice with a genetic defect, termed severe combined immunodeficiency, lack a functional immune system. Investigators have reconstituted the immune systems of these mice by implanting human lymphoid cells. The human cells that reside in the mouse can then be infected with HIV, creating a promising animal model called the SCID/hu mouse. These animals should be highly useful in studying the disease-producing effects of HIV and for evaluating the activity of potential drugs or vaccines against HIV. In addition, SCID mice naturally develop Pneumocystis carinii pneumonia, an opportunistic infection seen in AIDS patients. This model also enables scientists to study that disease and test the efficacy of potential new drugs. Additionally, uninfected SCID mice may be used to evaluate the effects of immune-stimulating therapies in intact animals.

The murine, feline, and simian retroviral models currently being used have proven to be valuable in confirming a drug's antiretroviral activity, in setting priorities for developing drugs for clinical trials, and for answering key questions regarding the dose, schedule, and use of a given drug. Complementing this effort is an animal model effort to evaluate therapies aimed at enhancing the immune response. Current and future treatments of HIV infections are likely to include these types of agents. These naturally occurring substances may prove to be highly effective in restoring the immune response or in decreasing toxicity associated with a given drug.

Research in murine, feline, and simian retrovirus model systems should continue to enable researchers to compare the activity of antivirals and immunomodulators in animal models with the activity of these agents in people infected with HIV. An important area for expansion is the inclusion of improved animal models using HIV. The SCID/hu and perhaps other immunodeficient model systems offer the unique potential to study the effects of therapies against HIV or other infections directly on human cells in vivo. The validity of these models for anti-HIV therapies will be determined as expeditiously as possible. The use of improved animal models will assure that compounds with the most promise are identified as rapidly as possible, appropriately prioritized for entry into clinical trials, and evaluated using a clinical protocol that optimizes the agent's chance for success.

The following are specific examples of the benefits derived from using animals in AIDS research:

IDENTIFICATION OF DRUGS TO TREAT PNEUMOCYSTIS IN PEOPLE WITH AIDS

Pneumocystis carinii is the most common opportunistic infection to cause disease in people infected with HIV. Attempts to grow Pneumocystis carinii in culture continue, but at present it has been work in animals that has led to an understanding of its biology, pathogenesis and, more importantly, ways to test for the ability of therapies to treat this disease. It was through the use of immunosuppressed rats infected with Pneumocystis carinii that the combination of clindamycin and primaquine was identified as a promising treatment for AIDS patients. Without this animal model it is unlikely that this combination would have entered clinical study.

EFFICACY AND TOXICITY STUDIES OF ANTI-RETROVIRAL DRUGS

Many critical questions with regard to the safety of a drug and its ability to block retroviral infections can not be answered in human trials for ethical and practical reasons. Studies in mice with AZT predicted the toxicities and efficacy of AZT in humans. Additional studies have answered key questions on the ability of AZT to inhibit the maternal transmission of the retrovirus from a mother to her unborn fetus or new born infant. Other studies in adult mice using a mouse retrovirus or HIV infected immunodeficient mice showed that AZT may greatly decrease or potentially block retroviral infections if given prophylactically.

The optimum dose of any anti-HIV drug that will maximize efficacy and minimize drug toxicity is not known. Animal models are providing key information with regards to the amount of drug to take over a given period and in what combination.

DEVELOPMENT OF A SUCCESSFUL VACCINE FOR HIV

The development of a safe and effective vaccine to prevent the spread of HIV infection is one of the highest priorities of the NIAID. The development of a vaccine will be difficult and, even if a candidate vaccine is identified, we may not know how effective the vaccine will be for years. Animals infected with SIV, a virus closely related to HIV, provide us with the best opportunity to quickly determine whether the design of a specific vaccine will protect the animal from a challenge with the live virus. Without the use of these models the effort to find a vaccine for HIV could be prolonged by decades.

ANIMAL WELFARE AND TERRORISM

Mr. **Weber**. Dr. Raub, have you made an attempt to quantify the costs to NIH both in dollars and in research, of complying with animal welfare regulations that have been placed on you? Also, how about the costs related to illegitimate acts, such as acts of terrorism extreme animal rights activists have perpetrated against NIH facilities?

Dr. **Raub**. The details of that I would need to provide for the record.

I will say now that, on the first issue, one of the major lines of expenditures in our buildings and facilities effort for NIH itself, is in meeting the standards associated with animal care and use. We have on the order of $18 million requested in the current budget as necessary to bring NIH to the point where we can meet those requirements.

Insofar as the break-ins are concerned, we have tabulated more than seventy instances where there has been a break-in, arson, destruction of property, theft, or other criminal acts, around the country in institutions. Normally when there is only theft of animals, the cost is said to be low. People tend to equate it simply to the replacement cost of animals. One of the things we have been attempting to do is to get law enforcement authorities to understand that it is not just the cost of the break-in. There may be years of research invested in those animals, and the theft can be valued at hundred of thousands of dollars.

When equipment is destroyed, the value of that is placed in the order of $50,000 or more. There has been a substantial bill resulting from that terrorist activity.

Mr. **Weber**. If you can provide that for the record, I will appreciate it.

Dr. **Raub**. I will be glad to.

[The information follows:]

Animal Welfare and Terrorism

The NIH has continued its efforts to improve the conditions of its intramural animal facilities to meet the high standards associated with the care and use of research animals as set forth in the Guide for the Care and Use of Laboratory Animals. The NIH recognizes accreditation by a private organization, the American Association for Accreditation of Laboratory Animal Care (AAALAC), as an excellent means of demonstrating institutional compliance with policies contained in the Guide. The NIH's institutional programs and facilities for activities involving animals will be evaluated for this purpose.

The major expenditures lie in the upgrading of our buildings at the NIH itself. The NIH will have invested $27.7 million by the end of FY 1990 in this effort and anticipates additional spending of approximately $43.7 million, including $18.5 million in the FY 1991 appropriation request and $25.2 million subsequently. If the NIH receives the FY 1991 appropriation as indicated in the President's budget, it will be in a position to seek AAALAC accreditation by December 1990, but must have plans to complete the renovation and upgrading of these animal facilities.

Insofar as the break-ins are concerned, the NIH is currently preparing to study the costs on a case-by-case basis of those instances where a break-in, arson, destruction of property, theft of animals, or other criminal act has been perpetrated by an animal rights group. The major categories of expenditures to be considered are: replacement of facilities, equipment and supplies; increased security; and investment(s) in the research project(s) affected by the act. In the latter case, the cost estimate includes the amount of support funds that would be lost if all or part of a project had to be repeated.

The NIH has reviewed the reports of 12 break-ins that occurred between 1982 and 1989 and estimated the total cost to be $4.6 million. However, this figure is derived from information reported to law enforcement authorities by institutional officials and is based solely on the purchase price of the animals, replacement of equipment, and repairs to the facility. In reality, the cost would be more accurate and significantly higher if it were based on the time and money invested in the conduct of the research itself.

The greatest cost--the loss of data or valuable information that might have been applied to the development of new or improved treatments and cures, thereby reducing human disability, suffering, and death--is incalculable. And in the long term, there are intangible losses, the disincentives to established researchers to continue their chosen profession and to young people entering careers in biomedical research.

In its March 1989 issuance of proposed rules affecting animal welfare, the U.S. Department of Agriculture estimated a cost of nearly one billion dollars to the regulated industry to comply with the requirements of the regulations. The Interagency Research Animal Committee, a group composed of representatives from several

Federal Government agencies that conduct biomedical research, has projected a Government-wide expenditure of over $40 million for facilities improvement.

Mr. WEBER. In addition to the direct costs in terms of dollars, researchers in my state tell me they are increasingly concerned about the human cost of personal intimidation by animal rights activists. They experience increasing stress along with their families because of the terrorist tactics of some of the most extreme animal rights activists. Is that a widespread concern in your judgment? Are researchers being intimidated both at work and in their homes?

Dr. RAUB. Yes sir, that is true. Many I know have been harassed not only at work but also at home. Their families have been threatened. I have been in the office of one of our grantees when a death threat came in on the telephone. It is a serious problem.

Mr. WEBER. I understand that in Britain where this sort of thing has gone on for a long time, research on animals is conducted almost under high security conditions. Do you know anything about that?

Dr. RAUB. The problem has existed much longer in the acute terrorist stage in the U.K. than anywhere else in the world. In some facilities, such as in private industry, they have found it necessary to work under extreme security controls as a way of guarding against vandalism and worse. We are hopeful it will not come to that in this country.

We not only have been concerned about security arrangements at NIH, but also have been working closely with the grantees on improved security and communications.

Mr. WEBER. I have a lot more questions along this area, and certainly the growing menace of animal rights groups is a concern I intend to raise again in the future.

Thank you very much.

Mr. NATCHER. Mr. Early.

NIH BUDGET REQUEST

Mr. EARLY. Dr. Raub, I have never seen an agency that has become more of a bureaucratic disaster. Over the last four years, I'm not sure that you've been totally truthful—or straightforward—at all. The chairman asked you what was needed for current services for 1991. You said $460,000,000. That would be current services for NIH based on funding for 1990. In your opinion, with regard to downward negotiation, isn't that a disaster?

Dr. RAUB. It makes a continuing series of challenges.

Mr. EARLY. With what you've had to absorb under with sequestration, isn't that awful?

Dr. RAUB. Ninety-six million dollars.

Mr. EARLY. What did you have to absorb with regard to the pay raises? It is not too favorable, is it?

Dr. RAUB. No sir.

Mr. EARLY. With regard to noncompeting grants, it has not been too favorable, has it?

Dr. RAUB. No sir.

DOWNWARD NEGOTIATIONS

Mr. EARLY. So you are telling Chairman Natcher that you need $460,000,000 for current services, and you don't have nearly enough money in 1990, isn't that right? OMB has taken over. As far as the autonomy that used to be there, the love of all the members, especially Mr. Natcher and Mr. Conte—they have been here a long time. They have seen it grow. I think that there are not enough breakthroughs, because you are not getting all the tools you need to do the job.

I want to focus on one thing to make my point—downward negotiation. Under the 1991 request it is anticipated that downward negotiation for competing grants will be 14.4 percent.

Dr. RAUB. Yes sir.

Mr. EARLY. For noncompeting grants it will be 10.1 percent?

Dr. RAUB. Yes sir.

Mr. EARLY. In '89 for competing grants it was 11.4 percent. For '90 it was 12.5 percent for competing grants. For noncompeting grants, Doctor, it was 9.5 percent in '89. This year it was 11.1 percent.

Dr. RAUB. That is right.

Mr. EARLY. We are not getting any breakthroughs. What is a typical size grant that you award to an investigator?

Dr. RAUB. About $200,000 in round numbers.

Mr. EARLY. Let's use that. Let's take the $200,000 grant. It was downward negotiated 9.5 percent or 10 percent in '89, using the Cancer Institute for example. So that $200,000 grant that you gave to, let's say, Columbia University, that $200,000 grant in 1989, went down to $180,000. Is that right?

Dr. RAUB. Yes.

Mr. EARLY. In 1990, the 11.1 downward negotiation, was that 11.1 percent applied to the $180,000 or was it applied to the $200,000?

Dr. RAUB. No, it would be 11.1 down from whatever had been recommended, which might have been $210 or $215.

Mr. EARLY. It might have been to what was funded, as the basis. So now you are going to downward negotiate again, by 10.1. These grants you are giving the institutes, that $200,000 grant, now in its third year, is now down to what?

Dr. RAUB. The way the budget is developed, typically there is an increase in the average cost.

Mr. EARLY. Doctor, you sound like an accountant. You give me a percentage increase and a downward—who ever heard of saying we are having a downward increase? What other agency does that? NIH now takes it as a standard thing.

I listened to Chairman Natcher ask how much could you possibly absorb by downward negotiation? The directors said the amount that would be disastrous would be ten percent.

Dr. Raub, do you recall that?

Dr. RAUB. I do.

Mr. EARLY. They suggested it should happen for only one year.

Dr. RAUB. That is correct.

Mr. EARLY. Well, it has happened every year now, for the last several years. How can we say we are doing anything with NIH? We are not filling the directorship because it does not have nearly the tools or authority that it used to have.

Dr. RAUB. I think that is certainly part of the perception.

Mr. EARLY. What is the main reason for downward negotiation?

Dr. **Raub**. The principal reason is that as we deal with an overall budget for research project grants, we try to ensure that we keep a reasonable balance between the number of competing research project grants, meet our moral commitment to the noncompeting grants and try to achieve at least a modest growth in current dollars from the previous year. It is a tradeoff among these considerations.

Mr. **Early**. What would your assessment be if I commented that that is diplomacy—where we give it to you and then they don't give it to you? How can they give it to you and know you are going to have to downward negotiate? Here is a group of dedicated people. All the people do not stay there for money, as Chairman Natcher mentioned. Five years ago, we were not doing too much with AIDS or the genome study. Now funds are mushrooming for these two areas and are being taken away from other places—they are not growing.

Now you come in with a new process. What are we doing with grants, calling them percentiles rather than pay lines? Or is it going to be percentiles represent the paylines? Aren't we doing something different?

Dr. **Raub**. Do you mean in terms of the terminology?

Mr. **Early**. Yes.

Dr. **Raub**. There are different terminologies in use as you have in our reports that try to explain it.

Mr. **Early**. I think that is just to confuse us. You've got a road map from OMB to destroy your agency. We give you a little more money, and we don't realize it is for more AIDS and the genome project, and the rest of the research suffers.

You are in here as if you had a pretty good budget. You have a disastrous budget, haven't you, Dr. Raub, for science, for what you are supposed to do? I'm aware of grantees that got $175,000 and they cannot keep their first assistants. Hasn't that happened to some?

Dr. **Raub**. Yes sir.

Mr. **Early**. Noncompeting grants don't have money for supplies, do they, Doctor? They are shrinking. It is disturbing what is happening in this particular area.

How are downward negotiations applied, Doctor, across the board to each grant?

Dr. **Raub**. Overall, there are some guidelines that each institute uses for that, but there is the expectation that our science administrators and grants management staff will look at each award to be sure that there is not an arbitrary reduction that would somehow be truly harmful to the project.

Mr. **Early**. Against the recommended funding level?

Dr. **Raub**. Typically they start with the level recommended by the councils, look at the level that now exists, and look at the many other tradeoffs in their research portfolios in their attempt to determine a funding level to sustain a momentum for that project.

Mr. **Early**. Does the actual award become the base to which it is applied?

Dr. **Raub**. It is always a point of reference in terms of the comparison of the level that is determined.

Mr. EARLY. I don't know what you mean, point of reference. Is it or is it not?

Dr. RAUB. Well, it is not a simple formula. The downward negotiation is normally applied to the recommended level not the actual award from the previous year.

Mr. EARLY. Nothing is simple OMB. I understand OMB's role, but your statement cites all that potential. We have been listening to NIH talk about tracing genes, crystallizing, signalling. Even I am starting to understand it. It is the same every year. We are not funding you to make progress. We are funding you to stay in business. That is disturbing.

Thank you, Mr. Chairman.

AVERAGE COST OF GRANTS

Mr. NATCHER. Dr. Raub, the grant shortfall has been made considerably worse, as you know, by a large increase in the cost of each grant. Your history tables indicate that the cost of a new grant will increase by 11.5 percent in 1990. How can NIH permit such a large increase in those costs when your budget is so limited?

Dr. RAUB. First, Mr. Chairman, there are several forces at work in terms of determining the cost of those programs. The largest single lost category in a grant is personnel. The increased costs are some manifestation of the increasing salaries in the research community. In some instances salary increases are necessary to compensate for earlier years and in others, salary increases are necessary to maintain a competitive posture with the emerging private industry.

In addition, as much of the work develops in molecular biology, we see it as being more labor-intensive than some other research. The number of individuals at post-doctoral levels has tended to increase for many grants. That is contributing to the increase.

We are dealing with ever more sophisticated instrumentation and ever more complex and costly supplies. All of those tend to add in the same direction in terms of the cost of our grants.

HISTORICAL COST OF GRANTS

Mr. NATCHER. Factoring both the increasing length of grants and the increased price, what is the expected total cost of a grant approved in 1990 compared with ten years ago?

Dr. RAUB. On a total basis, Mr. Chairman, a grant made 10 years ago would have been about $320,000. That is over the life span of the grant, which would have been just a little over three years. An award made today would be in the range of $800,000 for the life of the grant, where the average award today is a shade over four years. The increase in the length of the grant makes up for about $200,000 of that $500,000 difference.

INCREASE IN AVERAGE COST OF GRANTS

Mr. NATCHER. How do you explain, Dr. Raub, the situation in 1990 when we have downward negotiation of 12.5 percent and average cost increases of 11.5 percent? What do we have here?

Dr. **Raub**. We have again several factors at work, Mr. Chairman. First, they are a different set of grants than the grants that were awarded for the previous year.

Second, as we fund a lower percentage of grants, they tend to have a higher average cost. Typically the better the proposal is the more likely it will be at the high cost end of the spectrum and more likely that it will run for five years rather than three.

There is also some change in the mix of the grants in terms of the number that are research project grants of an individual nature and those that are program project grants. All of those factors, plus the inflation rate for biomedical research which runs a percentage or two above the general inflation rate, all work together to increase the average cost.

GRANT REVIEW PROCESS

Mr. **Natcher**. Is there any evidence that grantees are padding their budgets in anticipation of downward adjustments later on?

Dr. **Raub**. I don't believe there is any particular indication of that behavior. What ever temptation there might be to do that is more than offset by the realization of how stringent the competition is for funding. There are very few investigators who would put forward soft numbers or plans lest the review group not only cut out the excess, but also give them a less favorable score.

Mr. **Natcher**. Has NIH taken any steps to help the research community get through this lean period, especially new investors?

Dr. **Raub**. As a routine practice each one of the institutes pays attention to a variety of factors as they make their funding decision. Far and away the most important for everyone is the priority score arrived at by the study sections and the councils. As the institutes get near the margins of the funding, they take into account such things as whether this is a new investigator, an established investigator, whether there are multiple awards in that laboratory, or whether this award is the single one on which the laboratory depends.

This year in particular, many of our institutes have been giving even closer attention to those considerations. Overall, we find with the review system, first time applicants generally do rather well. Over the years, we were concerned theoretically that new people might not fare as well as the average. But the first time applicants generally are still well received.

GRANT APPROVAL RATES

Mr. **Natcher**. What percentage of grants which are submitted to NIH are approved by the study sections?

Dr. **Raub**. Approximately 95 percent, Mr. Chairman.

Mr. **Natcher**. Is a peer review system, which approves 95 percent of the applications doing its job, Dr. Raub?

Dr. **Raub**. It is something we have watched very carefully. On the surface that indicator might suggest there is easy grading or gamesmanship at work. We do not believe it is an indicator of a serious problem. We find, as competition has grown, that those who have a marginal interest in a research career have tended to drop out and the hardy souls have remained.

More than 30 percent of the applications in any given review round are revised applications from individuals whose idea was recommended for approval one time earlier, but missed funding. These individuals come in with a revised proposal built on the critique and recommendations of the previous review.

I cannot rule out the possibility that there are some individuals in the review system who will opt for approval with a knowingly unpayable score rather than outright disapproval. One of the reasons I believe that this could be at work to some extent, is that many individuals view the NIH review as a way of seeking funding from private sources.

It is often the case that our review groups would not want to give what they view as an unnecessary adverse rating lest individuals' other opportunities be cut off. Some institutions look at the individual faculty members' success or lack of success with NIH as one indicator for promotion.

In the main, I believe that the growing percentage indicates well prepared people with good ideas in a very stringent competition.

INDIRECT COSTS

Mr. NATCHER. What is the current average indirect cost rate at NIH? How much of NIH's budget is going to pay these costs in 1991, Dr. Raub?

Dr. RAUB. For research grants approximately 32 percent of award costs are indirect costs. That amounts to approximately $1.8 billion estimated for fiscal year 1991 out of a total of $5.6 for all research grants.

Mr. NATCHER. As you know, Dr. Raub, the Department of Agriculture has established a limit on indirect cost payments. Would this be appropriate for NIH grants as well?

Dr. RAUB. We have struggled for many years with this issue in concert with the leadership of academic institutions. Our feeling has been over the years that we should avoid arbitrary restrictions on the indirect cost levels. As our academic colleagues are quick to point out, these are also costs of research. They are labeled as indirect because of the near impossibility of allocating them to particular projects. But, nonetheless, the kinds of functions covered by the indirect cost payments are crucial to a strong research environment. We would proceed very cautiously with respect to any changes in the way any indirect costs are reimbursed or the introduction of caps or restrictions.

NOBEL LAUREATES

Mr. NATCHER. How many NIH supported individuals have won a Nobel Prize?

Dr. RAUB. The precise number is one I will provide for the record, but we must be approaching 100.

Mr. NATCHER. Would you insert in the record a list of all NIH related Nobel Laureates with the date of their award?

Dr. RAUB. Yes sir.

CLERK'S NOTE.—The attached list indicates the number to be 75.]

[The information follows:]

Nobel Prize Winners Supported by NIH Before Winning the Prize

Sidney Altman	1989
Thomas Cech	1989
J. Michael Bishop	1989
Harold E. Varmus	1989
Susumu Tonegawa	1987
Donald J. Cram	1987
Stanley Cohen	1986
Rita Levi-Montalcini	1986
Herbert A. Hauptman	1985
Michael S. Brown	1985
Joseph L. Goldstein	1985
R. Bruce Merrifield	1984
Henry Taube	1983
Sune Bergstrom	1982
John R. Vane	1982
Aaron Klug	1982
Roald Hoffmann	1981
David H. Hubel	1981
Torsten N. Wiesel	1981
Paul Berg	1980
Walter Gilbert	1980
Baruj Benacerraf	1980
George D. Snell	1980
Jean Dausset	1980
Herbert C. Brown	1979
Hamilton O. Smith	1978
Daniel Nathans	1978
Roger C.L. Guillemin	1977
Andrew V. Schally	1977
D. Carleton Gajdusek*	1976
Baruch S. Blumberg	1976
William N. Lipscomb	1976

David Baltimore	1975
Renato Dulbecco	1975
Howard M. Temin	1975
Albert Claude	1974
Christian de Duve	1974
George E. Palade	1974
Gerald M. Edelman	1972
Rodney R. Porter	1972
Christian B. Anfinsen*	1972
Stanford Moore	1972
William H. Stein	1972
Earl W. Sutherland, Jr.	1971
Julius Axelrod*	1970
Ulf von Euler	1970
Luis Leloir	1970
Max Delbruck	1969
Alfred D. Hershey	1969
Salvador Luria	1969

NIH Nobel Laureates (con't)

Robert W. Holley	1968
H. Gobind Khorana	1968
Marshall W. Nirenberg*	1968
Lars Onsager	1968
Haldan K. Hartline	1967
George Wald	1967
Charles B. Huggins	1966
Jacques L. Monod	1965
Robert B. Woodward	1965
Konrad Bloch	1964
James D. Watson	1962
John C. Kendrew	1962
Peter B. Medawar	1960
Arthur Kornberg	1959
Severo Ochoa	1959
George W. Beadle	1958
Joshua Lederberg	1958
Edward L. Tatum	1958
Dickinson W. Richards, Jr.	1956
Vincent du Vigneaud	1955
Thomas H. Weller	1954
Linus C. Pauling	1954
Fritz A. Lipmann	1953
Philip S. Hench	1950
E.O. Lawrence	1939

* NIH Scientist

BUILDINGS AND FACILITIES

Mr. NATCHER. Doctor, going to buildings and facilities, many of the buildings, as you well know, at the Bethesda campus were built in the 1950s. The Secretary confirmed at our hearing last month that many of these facilities will need major rehabilitation work during the next ten years. What is your best ball park estimate of the cost of these repairs, including the work at the Clinical Center?

Dr. RAUB. If we look at this on a ten year basis, in the way we did when I visited last fall with our advisory councils and boards, we estimate in round numbers an expenditure in the order of $1 billion. This amount would be required to ensure that the current buildings are brought up to the various codes and other performance standards, that our support systems for steam and chilled water and underground distribution systems are brought up to meet the performance standards that is required, that our animal facilities are developed and maintained at the levels necessary to ensure continuing accreditation for them, and that the Clinical Center undergoes the appropriate levels of renovation for everything from ensuring safety to making it more efficient to operate.

Within that $1 billion estimate, the most significant single variable is the cost associated with the Clinical Center. We are now working with a special committee to see if we cannot get a much more precise set of estimates and a long term plan with respect to the renovation of the Clinical Center.

Mr. NATCHER. Does NIH have an up to date facilities plan which reflects these needs?

Dr. RAUB. Yes sir, we do.

Mr. NATCHER. How much additional money will be required to complete the work on Building 49 and the Consolidated Office Building?

Dr. RAUB. For Building 49 we estimate an additional $38.5 million for the fourth and final phase of that construction effort.

For the Consolidated Office Building, the total estimated is about $133 million. As you know, there is just under $15 million appropriated for the first phase of planning for that building.

Mr. NATCHER. That would make it $118 million?

Dr. RAUB. Yes sir.

Mr. NATCHER. How much money is in your 1991 request for these new buildings?

Dr. RAUB. The 1991 request does not have funds in it for either of those two new buildings, Mr. Chairman.

Mr. NATCHER. Mr. Pursell, I yield to you.

SALARIES

Mr. PURSELL. I want to take a minute to discuss the salary issue. Can you supply the committee with—and I am not interested in the personality, but the slots in NIH that are paid over and above the Director's salary.

Dr. RAUB. Yes sir.

Mr. PURSELL. I don't need names, just the numbers and the positions.

Dr. RAUB. Yes sir.

[The information follows:]

EMPLOYEES EARNING MORE THAN THE NIH DIRECTOR

The NIH Director serves under one of two appointment authorities. If appointed under the Executive Level pay structure, the Director is paid at Level IV (currently $83,600). No bonuses or Physicians Comparability Allowance may be paid under the Executive Level. If appointed under the Commissioned Corps of the Public Health Service, the Director receives total compensation (base pay, specialty pay, living allowances) ranging from $56,991 to $114,192, depending on years of service and medical specialty.

NIH currently employs 291 employees whose annual Government salaries would exceed the current salary for the Director if the Director were appointed under the Executive Level (i.e., employees who earn more than $83,600). With only a few exceptions, these employees are physicians, who earn Physicians Comparability Allowance in addition to their base pay.

Following is a brief description of the types of the positions:

Senior Executive Service—57 employees

Typically these employees occupy such positions as ICD Directors, Deputy Directors or Associate Directors. In addition, some serve as world renown experts in a particular field of science or medicine. Some of the largest NIH laboratories are also directed by SES employees.

General Schedule—137 employees

These employees occupy a wide variety of positions at NIH including division directors, branch chiefs, laboratory chiefs, and section chiefs. Some of these employees are also renowned experts in a particular field.

Commissioned Officers—97 employees

These Commissioned Officers occupy a wide variety of positions at NIH including ICD Directors, Deputy Directors, or Associate Directors. They also function as division directors, branch chiefs and section chiefs.

Mr. PURSELL. We were discussing earlier that it would take legislative change to change the salary level. Can that be done on an appropriations bill without authorization?

Dr. RAUB. My understanding is that it could be. That would obtain a salary level change for strictly the one year life of the appropriations bill.

Mr. PURSELL. Are you aware of any increase in the House with respect to an authorization recommendation to upgrade that position?

Dr. RAUB. I am not aware of any specific legislative action on the position. There is under consideration in both House and Senate a larger pay system that would deal with biomedical scientists and that would include the Director of NIH. More important, it would include the array of senior scientists and senior science administrators that are critical to NIH operations.

Before the Pay Bill was passed, there was active consideration by the Department of Health and Human Services of a plan that would have addressed those salary needs as well. That plan is under reconsideration in the wake of the pay raise that the Congress voted last year.

Mr. PURSELL. Is there any particular authorization bill that looks at upgrading our institutes salary-wise?

Dr. RAUB. The Executive Branch has not taken a position yet on the particulars of any of the bills. It is still addressing itself internally to a plan HHS might be putting forward.

NIH DIRECTOR

Mr. PURSELL. But you are not on record as far as your position on any legislation with respect to this spending?

Dr. RAUB. The Department is on record as recognizing the seriousness of the problem. The major interest is manifest in the committee created by Dr. Sullivan, where he is looking for advice about the NIH Director position. There has been a great deal of discussion about salary, comparability, and the like. I don't believe the Department will take a position on these matters until that process is complete.

Mr. **Pursell.** When will that be complete?

Dr. **Raub.** My understanding is that the committee advising Dr. Sullivan is to complete its work perhaps by the end of April or early May. I expect the committee to make recommendations to him after the first of May. I have no way to predict with any certainty how long after that, the Department would decide to go forward with a proposal.

Mr. **Pursell.** So would you say May?

Mr. **Williams.** In that time frame.

Dr. **Raub.** May would be the earliest possible time.

Mr. **Pursell.** When is your earliest guess that you can get a full time Director on board?

Dr. **Raub.** If names were identified in the next six to eight weeks and the President was able to persuade an individual soon thereafter then depending on the confirmation process in the Senate, it could be sometime this summer.

Mr. **Pursell.** How long has that job been vacant?

Dr. **Raub.** Since the first of August last year.

Mr. **Pursell.** That is one full year. It is time to get it filled. I am sure it will be okay with you.

Dr. **Raub.** There are good days and bad days.

MAJOR SCIENTIFIC BREAKTHROUGH

Mr. **Pursell.** What would you outline as the NIH's greatest breakthrough this year? I know you named some in your report but if you were to select one. If I am asked by somebody back home, they would say Congressman, what did NIH do last year, what can I tell them?

Dr. **Raub.** In many ways it is easier to give you 30 than one. If I had to pick one, I would key on the joint effort by the National Cancer Institute and the National Heart, Lung and Blood Institute, which involved the first introduction of a foreign gene into human patients. This was part of an innovative approach to cancer treatment which is very exciting. In this instance, it became more dramatic because when the patient's own cells, that had been re-engineered, were re-introduced, a foreign gene was also introduced. This foreign gene served as a marker so the scientists could determine where the re-engineered cells went in the body.

The consequences are two part:

One is the demonstration of how powerful these immune system treatments can be for cancer patients. It has brought, in some cases, substantial progress for people who previously had no hope. In some cases, tumors disappeared. With the foreign genes, we have the beginning of human gene therapy.

The newspapers last week mentioned that the first proposal for human gene therapy is under review. We hope it will survive the many levels of necessary review and open a new era in medicine—

the ability to change the genome in a very precise way in a sick or disabled individual, and literally restore function.

RESEARCH CAREERS

Mr. PURSELL. Inasmuch as salaries have had some criticism, a lot of students at the University of Michigan are more interested in research than they are in medical practice. I am seeing a distinct change of going to research rather than practice. Do you see that?

Dr. RAUB. Yes sir, we think we are seeing the beginning of that as a national trend. There is no question, this is the most exciting time in the history of biology and medicine. We are hopeful as more people see the opportunities, that they will see a research career not only satisfying personally and intellectually, but where they can make a contribution to their world.

Mr. PURSELL. Most of the students I talk to seem to be excited about the future of research. Maybe they don't know all the real world provisions with respect to salaries and status in the biomedical research, but they seem to be moving toward that direction.

That says some good things for research. It doesn't say a lot for the medical field. We are having trouble finding a doctor in one of my counties for handling infant mortality cases. We really don't see any obstetricians interested in practicing anymore in large urban counties.

Thank you.

Mr. NATCHER. Mr. Stokes, I yield.

MINORITY SCIENTISTS IN EXTRAMURAL RESEARCH

Mr. STOKES. Dr. Raub, what is the level of participation of minority investigators in the extramural research program? I am talking about grants and contracts other than in the targeted programs? For example, can you tell us how many principal investigators holding regular research grants are black, Hispanic, Native American, et cetera.

Dr. RAUB. I cannot, Mr. Stokes, in that we have no way to collect that information associated with the research grant process. We don't have anything that is at all accurate or reliable.

Mr. STOKES. Last year you told the committee that you were going to undertake an effort to increase the number of minority investigators based on the recommendations of an advisory committee to the director of NIH.

One initiative was a supplement for minority investigators. Can you tell us the status of this initiative and how much will you put toward this initiative in fiscal 1990?

Dr. RAUB. This is an initiative that is being applied across NIH where essentially every one of our institutes is alert to opportunities where a minority investigator can be added to an on-going research team and where an administrative supplement could be provided.

I think last year we were in the range of $4,000,000 for that aggregate investment. We expect steady increases in that initiative as the opportunities become known to the minority scientists.

Mr. STOKES. How much are you requesting for 1991 for this?

Dr. RAUB. It is not a line item. It is part of the basic research grant budget. We would allow the level to be determined as the opportunities arise for the individual institutes.

MINORITY SCIENTISTS IN INTRAMURAL RESEARCH

Mr. STOKES. Each year, doctor, we discuss the number of minority researchers in the intramural research program. I have not received any encouraging reports on this matter. What can you tell us about that?

Dr. RAUB. One of the least satisfying statistics for us has been the relatively static picture over the years in terms of the number of minority scientists in that program. Over the last few years we have given attention to the recruitment end in terms of wanting to get more minority scientists into the staff fellow program.

We addressed ourselves to the disturbing thought that, up until last year, none of them converted to what we call a tenured status. Last year there were, I believe, four conversions in that group. In addition, we recognize that we need to not only put more emphasis on the recruitment but also to cast our net earlier in the educational system as a way of attracting members of various under-represented groups into our research program.

Mr. STOKES. Can you tell us how many black, Hispanic or Native American physicians are participating in the post-doctoral research training programs in the intramural program?

Dr. RAUB. For the staff fellows program in the most recent year there are 116 total minorities in the staff fellow program out of a total of 830.

Mr. STOKES. How many tenured medical officers do you have at NIH, Dr. Raub?

Dr. RAUB. In the commissioned corps at the highest levels, grade 6 through 8, there are at the moment six black and two Hispanic officers.

Mr. STOKES. That is out of how many tenured medical officers?

Dr. RAUB. Again, this is grade 6 through 8 of the commissioned corps where there is a total of 332 officers.

Mr. STOKES. How do these statistics compare with last year's figures?

Dr. RAUB. For the commissioned corps, this is actually a slight reduction from the previous year.

Mr. STOKES. You mean in terms of blacks and Hispanics?

Dr. RAUB. The Hispanics have remained constant. There is a loss of one member who is a black.

Mr. STOKES. How about Ph.D. staff fellows?

Dr. RAUB. The Ph.D. staff fellows number 830, as I mentioned earlier. The total of 116 minorities is made up of 24 blacks, 17 Hispanics, 75 Asians.

That 116 total is down from 131 in 1988.

MINORITY HOWARD HUGHES RESEARCH SCHOLARS

Mr. STOKES. How about your researchers participating in the NIH Howard Hughes Research Scholars program? How many black or Hispanic researchers do you have in that program?

Dr. **Raub**. I don't have those precise numbers with me. There are minority participants in that program as a result of activity on our part and that of the Howard Hughes Medical Institute, I will have to supply that for the record.

Mr. **Stokes**. Will you compare it for last year also?

Dr. **Raub**. Yes, sir.

[The information follows:]

Minority Howard Hughes Research Scholars

The table below identifies by race and sex the participants in the Howard Hughes Research Scholars Program in 1989 and 1990.

	1988/89	1989/90
Asians	6	12
Blacks	1	3
Hispanics	2	1
Women	17	16
Other	22	13
Total	48	45

MINORITIES IN MANAGEMENT

Mr. **Stokes**. Let me ask you about minority staffing, of those employees in management positions, GS or GM 14 and above, can you tell us how many are minorities, black or Hispanic and are you making any gains in this area?

Dr. **Raub**. This is the area of our most encouraging set of statistics. If we compare the end of 1988 with the end of 1989, that is, the end of the calendar years, in the GS 13 and above category for blacks, we grew from 141 to 155. For Hispanics, we grew from 33 to 37. If we look at that category of 13 through 15 over a two-year period, we find a set of numbers that I find encouraging.

Over that time, the total number of managers in terms of the net change, was a growth of 54 for all of NIH. That growth was more than accounted for by the increased numbers of minorities.

Specifically, there were 29 blacks, 10 Hispanics, one Native American and 15 Asians for a total net gain of 56 with a net loss of two in the non-minority categories. So essentially 100 percent of our net gain in those areas was made up by the influx of minority individuals.

We are encouraged by that statistic but realize that it is but the beginning of the kind of sustained effort that will be necessary to have a truly representative work force.

MINORITY RECRUITMENT

Mr. **Stokes**. As we discuss these areas, it occurs to me that obviously something dramatic needs to be done if we are going to make any meaningful impact in terms of equal employment opportunity for promotion where it comes to minorities at the NIH.

I know that you are aware of the program I initiated at the CIA and also at the National Security Agency. We initiated and passed legislation in the Congress to set up an undergraduate program where we get around the problem of the inability to attract bright young minorities into these agencies by setting up a program whereby these students receive assistance to attend colleges of their choice. For this program they have to meet a certain academic level. They are employed by the agencies through the summer months.

I am wondering if you are looking at any type of program of that sort for NIH and whether or not you think such a program would help make some impact upon this rather graphically dismal situation we have been talking about.

Dr. RAUB. We have been looking very hard at a set of options in this area for the reasons that you cite. We realize that, unless the pipeline has more qualified individuals in it, our options for recruitment will be very limited. We have given considerable attention to designing a NIH variant of the program that you mentioned for the security agency.

That program would identify young people as they enter undergraduate college and provide a means whereby their basic educational expenses could be met over the typical four-year period, and in addition, where they would have employment opportunities at NIH. In return for that, the idea would be that they would then work at NIH in a research activity. Or the obligation could be deferred if they had the interest in pursuing a graduate degree, to enable them to contribute at a still greater level in research.

These ideas are under consideration within the NIH and within the Public Health Service. It is premature for me to say in what form the program would emerge. There is interest on the part of the Assistant Secretary for Health and NIH in pursuing these ideas.

Another area is the reduction of the debt that physicians face at the end of their training. We had a special authority in AIDS research whereby physicians coming to NIH and working with AIDS research could have some of their indebtedness reduced by us in rough proportion to the amount of time they spend in our employ.

Again, it is premature for me to say there is a plan about to spring forward; but it is under active consideration at NIH and the Public Health Service. I believe initiatives of this kind will be necessary if we are to reverse the historical statistics.

Mr. STOKES. I am pleased to know you have these types of initiatives under consideration. Perhaps working together with this committee, we can help initiate some of these projects and hopefully be able to start a pipeline. Then we can bring in much better figures than we are all having to deal with at this time.

Thank you, very much.

Mr. NATCHER. Mr. Early, I yield to you.

AVERAGE COST OF GRANTS

Mr. EARLY. Dr. Raub, the justifications state that non-competing grants will receive an increase of 5.8 percent, and competing grants will receive an average increase of 2 percent. Now if we translated these figures into constant dollars, what would they be?

Dr. RAUB. The non-competing dollars are essentially equivalent to constant dollars if one uses the Biomedical Research and Development Price Index Deflator which is somewhat above the cost of living for the country in general.

Mr. **Early**. How is that a legitimate thing to do? I know we do it in this budget but wouldn't that be a much more legitimate figure to use, the BRDPI, rather than what you do use, in your scientific opinion?

Dr. **Raub**. We have used several figures.

Mr. **Early**. It is a simple question, doctor.

Dr. **Raub**. We believe the specific justification for that number is the strongest. There are many different views of it. We have provided all the numbers to be sure we are communicating.

HEALTH CARE COSTS

Dr. **Early**. What is the cost per person for health care for all Americans?

Mr. **Raub**. Off hand, I don't know.

Mr. **Early**. Would you put that in the record?

Dr. **Raub**. I will be glad to.

[The information follows:]

Health Care Costs

Total national health expenditures were $248.1 billion in calendar year 1980 and are projected to reach $661.3 billion by the end of 1990. This represents a 166.5 percent increase during the period. The corresponding per capita costs were $1,055 and $2,555, an increase of 142.2 percent. These calculations are based on data from the Health Care Financing Administration, the Social Security Administration and the Department of Commerce.

RESEARCH PROJECT GRANT AWARDS

Mr. **Early**. Doctor, in competing and non-competing grants, the justifications indicate that in the aggregate NIH will fund 123 more awards than in 1990, correct?

Dr. **Raub**. Correct.

Mr. **Early**. If you were to exclude the increase in AIDS and genome grants, how many more grants will you fund for all the other science that NIH supports?

Dr. **Raub**. Absent AIDS and genome?

Mr. **Early**. Yes.

Dr. **Raub**. Excluding AIDS and human genome the total would be 19,417 compared to 19,438 for 1990, a slight reduction of 21.

Mr. **Early**. It would probably be more accurate if we did it that way. Would you agree with the statements that grant proposals should be funded on the basis of scientific merit and the quality of the proposal?

Dr. **Raub**. Yes, sir, those need to be the principal considerations and always have been.

Mr. **Early**. Wait a minute, doctor. There is an article which reports that NIGMS is changing grant pay-out rules in an effort to fund more grants and contracts and that the council has adopted new guidelines that could redistribute some of the NIGMS grant money. Are any of the institutes going to use a means test to fund new grants?

Dr. RAUB. My understanding is that the council has been considering, at the margin of payment, the factor of whether this is the only grant the lab has or if there are multiple grants.

Mr. EARLY. So the answer is yes?

Dr. RAUB. Yes, but not exclusively.

Mr. EARLY. Doctor, I have no problem with you. You said something earlier with regard to trainees and the ones that stay in research.

You say the hardy sons stay in it. Aren't we at a point where the young investigators are not going into research because budgets like this don't show a future in it?

Dr. RAUB. That is certainly true with some individuals. One of our concerns with the intensity of competition is that young people with competence will, in fact, turn away to what they see as other ways to make their living.

CLINICAL TRIALS

Mr. EARLY. I hear it everywhere. In Massachusetts, I get lots of letters telling me what is wrong, which is rather simple given all the cuts you have in research. There is no future if we keep going down the road we have been going down, especially in the last four years given AIDS and the genome project.

Under the research grant mechanism what ramifications have downward negotiations had on the clinical trial projects?

Dr. RAUB. My understanding is that the effects have varied across the institutes. For some of them, the downward negotiations have been applied about the same way. For others, the projects can be at a stage where there is no way to make a reduction in it without a fundamental change in the design, reducing the number of patients or reducing the information being collected.

Many times the clinical trial, by its very tight design, offers very few opportunities to trim costs as opposed to basic science projects.

Mr. EARLY. That is tough.

You are narrowing and narrowing your trials to a point where I am not sure how good the data is going to be. What ramifications have downward negotiations had on clinical trial projects?

Dr. RAUB. That is a detail I would have to provide for the record because of the variants across the institutes, also there is the fact that across the institutes clinical trials are also funded through other mechanisms.

[The information follows:]

CLINICAL TRIALS

Clinical trials are a complex mechanism for supporting research. They have unique features from other research mechanisms, including being labor intensive and quite expensive. Trials are typically conducted in phases including recruitment, testing, follow-up, and data analysis. When research project grants are reduced through downward negotiations, the scope of a clinical trial may be reduced. In addition, in some cases progress is slowed which extends the length of the trial and causes delays in ascertaining the effectiveness of the treatment(s) the trial was designed to obtain.

Mr. EARLY. What effect will another year of steep downward negotiation have on clinical projects, in your opinion?

Dr. RAUB. I see two consequences. One is, to the extent that further reductions were required, there would either have to be a change in the scope of the study as I mentioned before or a delay in the initiation of further phases of existing studies.

COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENTS

Mr. EARLY. Are you saying they are needed? You and the other directors are not pointing out how devastating these cuts are. You can come up here with OMB represented at the table. You don't really perceive that we are getting just continuation of bureaucracy with downward negotiations year after year and not the breakthroughs the American people are entitled to.

Doctor, let's turn to page 3 in your statement, with regard to CRADAs. As Acting Director, doesn't that concern you. You have 100 cooperative research and development agreements with industry, and many more are being negotiated. With all the tools that the investigators are not getting in their third and fourth year of a non-competing grant, aren't you afraid they will leave for the private sector, and the private sector will reap the harvest?

Dr. RAUB. I need to disassociate the issues from the project grants and the CRADAs in that the CRADAs are tied to intramural NIH. We are positive about the opportunities that come from the amendments to the Federal Technology Transfer Act.

Mr. EARLY. Even in the intramural program, aren't you concerned when you don't have enough to do the job, given all the cutbacks. Everyone wants to succeed. Are you concerned that you may be giving private industries too much?

Dr. RAUB. The positive side of the CRADA arrangement, in the spirit of that law, was ensuring that the results would be commercialized and that we would build good working ties to the industry and the industries would be able to contribute people and equipment as part of a shared effort.

The concerns are not financial ones, they are philosophic. That is, we want to be sure that only projects that are right for that activity are indeed being approved. In the long term we want to be sure that our leading scientists keep focus on the best research opportunities and are not drawn just to those they might think will have a quick commercial impact.

So far so good, I believe. But it is important for us to be sure that the CRADAs are properly balanced.

BUILDINGS AND FACILITIES

Mr. EARLY. The Chairman brought up construction. We talk about it each year. You said in your statement "furthermore the conditions of NIH boilers, chillers and steam lines have reached the critical point where the useful life for these vital facilities is ending."

Isn't that really threatening?

Dr. RAUB. Indeed it is. That is the reason we are placing the highest priority in this budget on the $88,600,000 sum. We would be able to begin reducing those problems before indeed they become crises.

Mr. EARLY. They have already become crises according to your statement. It is a question of when they will explode.

Thank you, Mr. Chairman.

AIDS VS. NON-AIDS FUNDING

Mr. NATCHER. Dr. Raub, last year the committee attempted to give NIH more flexibility regarding specific amounts for AIDS versus non-AIDS research. Was this the right thing to do?

Dr. RAUB. Yes, sir. I think all the institutes have appreciated the flexibility to make some fine tuning of their expenditures as they face the particular opportunities and challenges of the year rather than in advance.

Mr. NATCHER. Is NIH using this flexibility in allocating these funds in 1990?

Dr. RAUB. Yes, sir.

RESEARCH TRAINING

Mr. NATCHER. Under training, Dr. Raub, if you would, review for the committee just briefly the recommendations made by the National Academy of Sciences in its new report on research training needs in the biomedical sciences.

Dr. RAUB. The report to which you are referring is the one issued every four years by the National Academy of Sciences looking at the needs across biomedical and behavioral research with special emphasis on emerging areas such as biotechnology.

In this instance, the committee recommended total numbers of training positions for NIH and some components of the Public Health Service. There is somewhat of a discrepancy between the Academy's numbers and ours. We believe the difference has to do with the bases of the projections used. We see the report as a strong reaffirmation of our need to be in the research training business and for us to continue this as a major part of NIH activity.

Over the coming months we will be reviewing the recommendations of that group along with the recommendations of an in-house study led by Drs. Lenfant, Kirschstein, and Kupfer. The in-house study contains a series of steps, some of which we have begun to implement and others we have had under consideration for future budget submissions and/or legislative proposals that will help us match our training efforts to the needs of the 1990's.

Mr. NATCHER. This new study recommends that the Federal Government provide 11,670 full time training positions in 1991. How does this compare with your budget proposal for 1991?

Dr. RAUB. Our budget proposal requests a larger number of trainees, 12,020 to be specific. The difference is in the base from which we project, not any fundamental disagreement between us or the Academy as to the nature of need. Our figure includes short-term trainee figures and the Academy's does not.

The Academy worked with an estimated figure which was modified upward and we were working with the latter figure.

Mr. NATCHER. The Academy has changed its method of counting training slots. Please insert a full statement in the record reconciling the differences between the way they count trainees and the system used in the budgetary request.

Also, Dr. Raub, discuss any other problems with the methodology which they have used. Place that in the record.

[The information follows:]

NAS RESEARCH TRAINING REPORT

The National Institutes of Health's analysis of the National Academy of Science report of the Committee for Biomedical and Behavioral Research Personnel indicates three potential sources for this difference.

First, the Academy used estimated figures for 1987, their baseline year. Their calculation of 9,490 for NIH alone is well below 10,624, the actual number of full-time training positions (FTTP) funded by NIH in FY 1987. In making projections they appear to have compounded the shortfall of 1,134 for FY 1987 into one of 1,440 in FY 1991.

Second, the Academy excluded short-term (three month) research training (T35s) while NIH includes these awards in its estimates calculating them on a four for one basis.

Third, in developing its projections the Academy used a database different from the one used by NIH in calculating FTTPs for 1991. The two databases differ by approximately fifteen percent with the Academy's projections being lower than those from the NIH.

Even though there are differences in the absolute numbers contained in the report and those used by NIH in its budget request, it is important to note that the levels recommended by the Committee represent increases in the number of FTTPs of approximately three and one-half percent per year between 1989 and 1993.

RESEARCH TRAINING STIPENDS

Mr. NATCHER. The committee is aware that NIH has conducted its own study on training which, among other things, recommends a substantial increase in stipends. What would this cost to implement in 1991?

Dr. RAUB. Our preliminary analysis suggests on the order of $39,000,000. That is one of the issues that we have under consideration right now for future proposals. The report of our in-house study has been shared with all of our national advisory councils and boards at their last round of meetings. We are now getting their ideas and recommendations.

There will be further attention paid to this in early June at a meeting of the advisory committee to the NIH Director. We are giving all of these recommendations, including the stipend increase, very serious consideration.

Mr. NATCHER. Are funds included in the 1991 budget to increase stipends?

Dr. RAUB. No, sir. The 1991 budget proposal maintains stipends at the current levels.

PHYSICIANS' RESEARCH TRAINING

Mr. NATCHER. The Academy's report indicates that only 8.5 percent of the M.D.'s who receive NIH training support ever apply for a research grant.

If this is true, doctor, something seems very wrong with this training program. What can you tell us about it?

Dr. RAUB. In the main we share your conclusion about that, Mr. Chairman. As we have studied it over the years it has become quite clear that the traditional training grant is the least efficacious means we have to attract and to keep physicians in research careers.

Indeed a major part of the motivation behind the in-house study which I mentioned, was looking at some causes and alternatives we might pursue to make research training of physicians more effective.

For many physicians, a one-year training experience is inadequate to be able to compete with better trained individuals, both physicians and Ph.D.'s. One of the things under active consideration is a requirement that the training experience be at least two years.

Another of the ideas put forth by Dr. Lenfant and his colleagues was to modify provisions permitting an easy coupling of the traditional training grant and our research careers program, resulting in a grant which provides a guided research experience for a junior scientist.

If we could get some people to take two years of training and then move easily to a three-year experience as a clinical investigator, perhaps under the guidance of a mentor, then we might be more successful in having these individuals become scientists in their own right than has been historically the case.

STAFFING

Mr. NATCHER. Doctor, we go next to staffing. The budget documents indicate that NIH will increase staffing by 929 full time equivalent positions in 1990 and 1991. Tell us how these positions will be utilized and how you managed to get an increase for 1990.

How did you manage that, Dr. Raub?

Dr. RAUB. May I start with the second part first?

Mr. NATCHER. Go right ahead.

Dr. RAUB. As we have developed our case within the Department for additional full-time-equivalent positions, the Department has been willing to remove some of the previous strictures where FTEs were budgeted and managed separately from the funding. Instead, the Department has given us encouragement to employ the number of FTEs that funding would allow.

The additional flexibility has made it possible for some increase in the FTE count. The purposes for which they would be used are many but special emphasis has been placed on certain emerging needs—the genome project and in AIDS in particular. The FTEs would also be used to address needs across the board since every one of the institutes suffered declines in the number of people on board from the mid 1980's.

So much of the FTE increase in 1990 has been directed toward a restoration of the previous losses.

Mr. NATCHER. Doctor, where did you find the money for the additional full time positions in 1990?

Dr. RAUB. We worked within the accounts budgeted for personnel and program services and made the appropriate trade-offs in terms of personnel expenses against the other types of supporting nonpersonnel costs in those categories.

Mr. NATCHER. Can you tell the committee how many of these new positions in 1990 and 1991 will be for AIDS activities?

Dr. Raub. The change from 1989 to 1990 for AIDS is 309 out of a total of 575. In going to 1991, we propose that 111 of the 354 be allocated to the AIDS activity.

Mr. Natcher. What is the top salary expected to be paid in 1991 for NIH's best scientists and administrators?

Dr. Raub. If I may, Mr. Chairman, I will give a two-part answer to that. The vast majority of our scientists are at Level 4 in the Senior Executive Service. In 1991 if the pay raise materializes as the law now provides, the base salary for that level would be $97,000.

If those individuals are physicians they would be eligible for a $20,000 physician comparability allowance, assuming that the PCA authority, destined to expire at the end of September of this year, is renewed.

Those senior scientists would be receiving a salary of $117,000. That might or might not be supplemented by a performance bonus depending on their performance relative to their colleagues.

That bonus could be $5,000 to $10,000, or in rare cases, $20,000. The pay cap that would apply in any case would be Executive Level I which is $134,100.

The other part of my answer is that, at the very highest, the very best we could possibly do would be Senior Executive Service Level 6 at which we have only one employee. That would be $104,500. If that individual was also a physician, the salary could be supplemented by $20,000 which would make the total salary $124,500.

ENDOWED RESEARCH CHAIRS

Mr. Natcher. Explain to the committee how your proposal for 10 endowed research chairs would be administered.

Dr. Raub. That recommendation stems from the Institute of Medicine study of our intramural program recognizing our inability, over the last 11 years, to recruit anybody into the science positions at the senior level.

The idea is that with such a fund we would be able to supplement the standard government salary of up to 10 senior scientists as a way of attracting and keeping those individuals.

The funds in excess of the standard government salary for the endowed chairs would have to come from private sources. The appropriation proposal is designed to put NIH in a position to receive sufficient funds, albeit not solicit them, and then apply them to supplement government salaries of up to 10 scientists, to the extent funds were available.

Mr. Natcher. Doctor, would the existence of these higher paid chairs create dissension among other top people at NIH who are paid somewhat less?

Dr. Raub. We would certainly face the possibility of such dissension. As indicated by the numbers I mentioned earlier, there is now a considerable range of salaries that does not always correspond with one's seniority or responsibilities. If we were to administer the endowed chairs without considering some of our own high quality scientists, as well as non-NIH scientists, we could create dissension. It would have to be administered very carefully.

Mr. NATCHER. Mr. Pursell, I yield.

Mr. PURSELL. I think there is a lot of dissension. There is a lot of morale problems when the director is paid less than people below him or her. That seems to be a serious defect in the character of the institution. How many people have turned that job down?

Dr. RAUB. I have no way to know that with any certainty.

Mr. PURSELL. You could not tell me, two, three, five?

Dr. RAUB. The newspapers indicate three or four, but I have no first-hand knowledge of that.

Mr. PURSELL. Could you get Dr. Sullivan and the department to make a salary adjustment without congressional appropriation or authorization change, make a recommendation?

Dr. RAUB. To the best of my knowledge, it would require legislation.

Mr. PURSELL. But we could do it as a committee.

A lot of researchers back at the university sometimes question the wisdom of an institute versus initiatives in creating biomedical research.

Do we have 16 institutes?

Dr. RAUB. We have 13 institutes so named, and five other components.

DECENTRALIZATION

Mr. PURSELL. Does that jeopardize policy wide where the country should be in terms of research based on national priorities? Do you think the incremental adjustments within the institutes each year based on the budgetary constraints of the federal budget create good creative research nationally in a more decentralized market oriented society with competing interests?

Dr. RAUB. I don't think there are any significant barriers to creativity as far as the organization is concerned. One can make a strong argument that much of NIH's strength and success over the years is because it has been so highly decentralized and the individual components have been so tightly tied to the scientific and clinical constituencies as well as the public constituency.

The difficulty is in the overall management and coordination of the multiple entities with their individual missions and traditions.

The ever present concern as new components are suggested, is to be sure more is gained than lost by the additional dimensions or fragmentation of the effort.

NATIONAL BIOMEDICAL PRIORITIES

Mr. PURSELL. Based on the advancement of computerization and advancement of technology, coordination, are we doing a relatively good job in coordinating the thrust of our national biomedical priorities given the intramural, extramural, university settings?

Are we controlling that enough so that we are making a major thrust in the proper priorities or we are ending up with some duplication and some missing links in our national priorities?

Dr. RAUB. I think we are doing very well on that score. Each institute has its own planning process based on the national advisory council. Each pays close attention to setting those priorities in terms of needs and opportunities.

In addition, our peer review system remains second to none in terms of ability to detect and recommend ideas that seem to be most seminal and creative in advancing science on a broad front.

There is strong communications and coordination within the NIH. As you read the statements of our various institute directors, you will find example after example of confluent interests and coordinated efforts to be sure there is no duplication or oversights.

There is an increasing number of collaborative efforts as the areas of science come together.

Mr. PURSELL. So you think there is enough checks and balances in the system to give us a quality program?

Dr. RAUB. Yes, sir.

Mr. PURSELL. If you were to make an improvement in any of that, where would you make it, outside of additional salaries?

Dr. RAUB. In terms of communication and information, there are things we could improve such as more timely sharing of information and closer targeting of possible joint efforts. Other than pursuing those lines, I don't believe there is anything fundamentally different that we could or should be doing.

NEW INSTITUTES

Mr. PURSELL. There are some proposals floating around for additional institutes. How do you feel about that?

Dr. RAUB. I think each one needs to be considered on a case-by-case basis. The first question is: what is the research agenda that would be carried out by that new entity? The corollary question is: to what extent can we meet that agenda within our current frame work? There have been times when we have been concerned about the effects of a new entity decoupling from its original component.

Mr. PURSELL. Do you think historically creation of a new institute threatens and jeopardizes the rest of the institutes with respect to funding?

Dr. RAUB. Not necessarily. If one looks at the history of NIH, one can make a case that it was creation of a new entity that established a new magnet for the public interest. In more recent years, when the competition for funding between research and other programs of the federal government has been so severe, many have expressed the concern that the creation of a new entity, at least in the short term, increases fragmentation and the complexity of management.

The creation of each of these new entities has been so different in its merits, I don't believe one can generalize.

Mr. PURSELL. You don't believe there is an opportunity to expand the creativity of the institutes, to maximize the biomedical research with proper guidelines to give us—I am thinking of other federal policies with respect to $1.00 federal money matching $5.00 private sector money.

That gives us the domino effect of bringing together more private university funds to put together with the federal level which I think is very limiting.

Frankly, I think $8,000,000 is a very small number for a nation of this size. Of course, I am not adding up the universities and house budgets that have money set aside for this. Aren't there ways creatively that we can improve this component aside from the federal piece here?

Dr. RAUB. As the Chairman noted in opening the hearing, the percentage of the total research effort for which NIH is responsible has dropped even though the absolute dollars have increased. A major part of the reason for that is the opportunities in science, molecular biology and biotechnology that came out of the NIH funding. Within the last decade, in particular, private industry has had more incentive and greater expectation of pay off in making larger R&D investment, than, say, in the 1970's. The bulk of those commercial investments are in-house, and primarily at the development end of R&D rather than basic science.

The biotechnology industry is the exception. In small companies one finds the target blurring because of the way molecular biology can be turned so quickly to application. A second development has been increasing ties between universities and industries as a result of the 1980 amendments to the patent and trademark act, providing new incentives for universities to pursue the commercialization of research results in cooperation with the private sector.

For some of the research-intensive universities that have created a new revenue stream, the product produces royalty money that can be used in the programs of the institution. However, even the most successful of those institutions derive only on the order of 5 percent of their overall revenues from their commercial contacts. So it would not be likely to displace their dependency on NIH, especially in basic science.

INTERNATIONAL RESEARCH

Mr. PURSELL. Do you see any creative ideas internationally, in other countries, in the area of this research?

Dr. RAUB. Other nations differ from us in certain ways. One, we are far and away the principal investor in basic science. Other nations have moved less dramatically and more slowly in terms of that investment. On the other hand, some other nations have a different social history in terms of the way their public and private entities interact, particularly Japan.

We have some lessons to learn in terms of how public and private activities can mesh rather than be kept separate. I think it has a lot to do with the way research results are translated into commercial applications and with our overall competitiveness in the biotechnology industry.

RESEARCH AGREEMENTS WITH EASTERN BLOC

Mr. PURSELL. Do you see a closer relationship with the Soviet Union in light of recent history in terms of biomedical research?

Dr. RAUB. Most likely yes, not only with the Soviet Union but with the other countries of the Eastern Bloc. We have had a series of collaborative agreements for many years with the Soviet Union, Hungary and other nations.

We see new opportunities not only for joint research projects but particularly for studies that can be done uniquely in those countries, especially as it relates to public health. We will be alert to taking advantage of those opportunities.

INTERNATIONAL AIDS EFFORT

Mr. PURSELL. Is there a good coordinated world health organization coordination in things like AIDS notwithstanding other coordinated efforts to address that issue?

Dr. RAUB. I believe there is good coordination.

Dr. FAUCI. Also, NIH representatives have recently visited Russia with the thought of increasing and intensifying the collaboration in basic research and also in AIDS research. That collaboration will spill over to the Eastern European countries also.

Mr. PURSELL. Are they having a serious problem?

Dr. FAUCI. They have a growing problem. They have had some real catastrophes with infants and children becoming infected with AIDS from contaminated devices. It has been a serious problem, particularly in Romania and Russia. We are realizing the magnitude of the problem now that they are admitting to its existence. They are approximately where we were several years ago in the escalating curve of infected people.

With the opening of the borders and increased travel between East and West, it is only going to get worse, and they realize that.

Mr. PURSELL. The proposal of the Soviet Union is broader than just one subject?

Dr. FAUCI. Yes, it is.

Mr. PURSELL. Comprehensively, what are we suggesting right here?

Dr. FAUCI. We are suggesting scientist-to-scientist collaboration which really has not been very well implemented in the past. Also, we are suggesting joint programs whereby their investigators train here and become involved in collaborative projects.

Mr. PURSELL. Thank you, very much.

Mr. NATCHER. Mr. Early, I yield.

BASIC RESEARCH

Mr. EARLY. You just told Mr. Pursell that we in this country are the primary investors in basic research. In the last five years if you had a multiple choice question of has our lead stayed the same, increased or decreased, what would you check?

Dr. RAUB. I would say it stayed the same. With some countries it has decreased.

Mr. EARLY. With regard to Japan, haven't they made more of a commitment to basic research? If you separate Japan from West Germany and us, five years ago wouldn't they have been closer to what we are doing?

Dr. RAUB. There have been major percentage gains but their base was much smaller.

Mr. EARLY. In terms of constant dollars, have they done more?

Dr. RAUB. Yes, in terms of constant dollars.

SALARIES

Mr. EARLY. How about salaries, about which Mr. Pursell and others asked you. As you know NIH has always been a low payer for the best people. The gleam or luster in NIH is diminishing, in my opinion. If you had another multiple choice question which asked is it because of the low salaries, downward negotiations, training, being on a roller coaster, what would be checked?

Dr. RAUB. For the NIH program itself, that is, the intramural program, only the salary level applies. More than any other single factor for the senior scientist, salary level is the major problem.

Mr. EARLY. Do you think the senior scientist would have more of a problem with the lack of salary, uncertainty about FTEs, uncertainty about trainees, the roller coaster, the uncertainties with regard to autonomy.

Dr. RAUB. I think the senior scientists at NIH are most concerned about their salary position relative to the opportunities that they have on the outside.

They are also concerned about their means to do research, that is the kind of facilities and support we provide for them. We have been able to keep as many as we have because NIH is still a wonderful place to do research and there are opportunities that we can provide that are difficult to match elsewhere.

EXTRAMURAL CONSTRUCTION

Mr. EARLY. That answer surprises me.

Doctor, we gave you $15,000,000 for extramural construction grants. You tapped all the institutes to see what they needed; right?

Dr. RAUB. That is true.

Mr. EARLY. How about NCI.

Dr. RAUB. They have been assessed $3,500,000.

Mr. EARLY. How much did you give them?

Dr. RAUB. The allocation is not complete. The first part of the allocation of those funds was $2,000,000 for NCI, for some nationally competed and reviewed high priority construction projects. In the remaining period there will be other proposals, especially for NCI.

Mr. EARLY. How much of the money is left?

Mr. RAUB. The balance is $12,800,000. The original $15,000,000 was reduced to $14,800,000 because of sequestration. There remains $12,800,000 in competition.

Mr. EARLY. Do the other institutes have requests in?

Dr. RAUB. The requests will come from the outside in terms of grant applications responding to our solicitation. They will need to fall within our construction authorities, of which there are four. One is a special authority passed last year by the Congress for a mouse breeding facility. That is something of interest to virtually each of the institutes because of the importance of special strains of mice, especially mutant strains in our programs.

We have construction authorities in the National Heart, Lung, and Blood Institute and also the National Eye Institute as well as the Cancer Institute. Within as broad a reading as is appropriate in those authorities, we will be entertaining proposals for construction grants.

Mr. **Early.** I would prefer to see that go directly to the institutes. There's too much back and forth when it goes into the director's office. Would you comment?

Dr. **Raub.** I think there are pros and cons. In this particular case, the only way that we could meet all of the conditions of the legislative history was to assess the several appropriations, create a central fund and then run the national competition. There is much to be said, however, for direct appropriation of construction funds to the individual institutes to make decisions within their priorities.

For that to be broadly effective, every one of the institutes will need to have construction authority and only three do now—the National Cancer Institute; the National Heart, Lung, and Blood Institute; and the National Eye Institute.

DECENTRALIZATION

Mr. **Early.** I am an advocate for independence among the institutes. That is what I always thought was a strong point of the NIH. You said something about centralization to Mr. Pursell. I got the impression that you were for decentralization. You cannot have it with these budgets, can you?

Dr. **Raub.** I think there are strong reasons, as I indicated to Mr. Pursell, for decentralization. In this particular instance, given the amount of money involved, the legislative history, and the intense competition we know we are going to have for the funds, operating it as a central program made the most sense.

Mr. **Early.** I have some questions that I will submit for the record.

Thank you for the testimony.

Mr. **Pursell.** Make sure you add the nurses to the list.

Dr. **Raub.** We will.

Mr. **Natcher.** Dr. Raub, this committee has frequently asked you for your advice in allocating funds among the NIH programs if the committee can come up with additional sources. We want you to do the same for this year. We want you to submit to the committee a plan for allocating $500,000,000 in $100,000,000 increments. This should cover all activities except facilities' needs at NIH itself which we will deal with separately.

If you will do that, Dr. Raub, submit that now. It will help us.

[The information follows:]

BUDGET PRIORITIES

ADDITIONS OVER THE FY 1991 PRESIDENT'S BUDGET

1st $100 Million Increment

- Provides $86.3 million for 349 additional competing research project grants and reduces FY 1991 downward negotiations from 13.4 percent to 12.0 percent. Slight increase in noncompeting research project grant funding to reduce downward negotiation rate from 10.1 percent to 10.0 percent.

- Provides approximately $2.1 million to increase research career awards, research trainees, contracts, and to supplement intramural research and research and management support.

- Provides $64 million for research centers and for additional clinical trials.

2nd $100 Million Increment

- Funds an additional 152 competing research project grants and reduces downward negotiations further, from 12.0 percent to 10.9 percent. Slight increase in noncompeting research project grant funding to reduce downward negotiation rate from 10.0 percent to 9.9 percent.

- Funds an additional 119 research career awards and 469 research trainees, primarily in the predoctoral area.

- Funds additional clinical trials.

- Provides funding to research centers for inflationary increases, and for selected expansion. Adds funding to cover inflation and selected expansion for contracts, other research grant awards, intramural research and research and management support.

- Targets funding for the Fogarty International Center for their international fellowship programs, the National Library of Medicine for the medical library assistance program, and the National Center for Research Resources (previously the Division of Research Resources) for their Biological Models and Materials Research Program, General Clinical Research Centers, and Primate Research Centers.

- Provides funding for the National Cancer Institute's cancer control program and for construction and renovation of cancer research institutions, including the Frederick Cancer Research Center.

- Provides funding for the Academic Research Enhancement Award program.

3rd $100 Million Increment

- Funds another 152 competing research project grants and reduces FY 1991 downward negotiations further from 10.9 percent to 9.6

percent. Noncompeting research project grant funding increases, resulting in a decrease in downward negotiations from 9.9 percent to 9.7 percent.

- Provides funding to increase slightly the number of research career awards and research trainees.
- Provides funding to increase the number of clinical trials.
- Provides funding to research centers for inflationary increases, and for selected expansion. Adds funding to cover inflation and selected expansion of contracts, other research grant awards, intramural research, research and management support, and the Office of the Director.
- Provides $1 million to initiate the establishment of an NIH Graduate University. This would require the inclusion of authorizing language.
- Targets funding for the Fogarty International Center for additional international fellowships (Latin American and Eastern European initiatives) and additional scholars in residence, the Library of Medicine for their medical library assistance program, and the National Center for Research Resources (previously the Division of Research Resources) for their Biological Models and Materials Program, General Clinical Research Centers, and Primate Research Centers.
- Provides funding for the National Cancer Institute's cancer control program and for construction and renovation of cancer research institutions.
- Provides funding for the Academic Research Enhancement Award program.
- Provides additional funding for AIDS research.
- Provides funding to establish a new minority program to increase recruitment of minority students by subsidizing their college expenses. This program would require the inclusion of authorizing language.
- Provides funding to establish a loan repayment program to assist students in repaying their academic loans, in exchange for their participation in NIH non-AIDS research. This program would be the same as the program established in FY 1990 for the AIDS program. Authorizing language would be necessary.

4th $100 Million Increment

- Funds an additional 119 competing research project grants and reduces FY 1991 downward negotiations further from 9.6 percent to 8.6 percent. Noncompeting research project grant funding increases to reduce decreasing downward negotiations from 9.7 percent to 9.5 percent.
- Funds 19 additional research career awards and 100 additional research trainees.

- Provides funding to increase the number of clinical trials.
- Provides funding to enhance efforts supported through research centers, contracts, other research grant awards, intramural research, and research and management support.
- Targets funding for program enhancements in the National Library of Medicine for medical informatics and for the National Center for Research Resources, for their General Clinical Research Centers, shared instrumentation grants, and animal facilities improvement grants.
- Provides additional funding for AIDS research.
- Provides funding to raise the salary cap on research career awards.

5th $100 Million Increment

- Funds an additional 77 competing research project grants and reduces downward negotiation slightly from 8.6 percent to 8.4 percent. Funding for noncompeting awards increases slightly with downward negotiation decreasing slightly from 9.5 percent to 9.4 percent.
- Provides funding for an additional 76 research trainees.
- Provides enhanced funding for research centers, contracts, other research grant awards, intramural research, and research and management support.
- Provides additional funding for the National Cancer Institute's construction and renovation of cancer research institutions.
- Provides additional funding for AIDS research.
- Provides funding to increase stipend levels for research trainees.
- Provides extramural construction funding with emphasis on minority academic institutions. This program would require the inclusion of authorizing language.

DHHS - NATIONAL INSTITUTES OF HEALTH
Allocation of an Additional $500 Million
by Mechanism and by $100 Million Increments
(Dollars in thousands)
Increases Over FY 1991 Request
Includes AIDS

RPGS:	FY 1991 Pres.Bud. Request	First $100,000 Increment	Second $100,000 Increment	Third $100,000 Increment	Fourth $100,000 Increment	Fifth $100,000 Increment	Total +$500,000
# Noncompeting	15,292	15,292	15,292	15,292	15,292	15,292	15,292
# Competing	5,044	5,393	5,545	5,697	5,818	5,893	5,893
Noncompeting D.M.	-10.1%	-10.0%	-9.9%	-9.7%	-9.5%	-9.4%	-9.4%
Competing D.M.	-13.4%	-12.0%	-10.9%	-9.0%	-8.6%	-8.4%	-8.4%
Award Rate	25.2%	26.9%	27.7%	28.4%	29.0%	29.4%	29.4%
+ Noncompeting RPGs	---	5,209	3,756	8,078	8,300	2,914	28,257
+Competing RPGs	---	86,256	39,648	35,646	30,059	16,904	208,513
Subtotal , RPGs	---	91,465	43,404	43,724	38,359	19,818	236,770
+Research Careers	---	600	8,245	235	1,225	---	10,305
+Research Training	---	116	8,885	1,053	2,938	2,139	15,131
+Clinical Trials	---	2,500	2,500	10,360	9,281	---	24,641
+Centers	---	3,906	13,770	12,733	7,159	4,293	41,861
+Contracts	---	600	1,575	5,156	6,089	3,347	16,767
+Intramural Research	---	500	3,646	1,000	4,637	2,248	12,031
+RMS	---	313	805	4,200	1,000	1,303	7,621
+FIC	---	---	1,000	1,000	---	---	2,000
+NLM	---	---	2,000	1,000	1,000	---	4,000
+Natl Ctr for Res Resources.	---	---	6,000	7,000	3,675	---	16,675

DHHS - NATIONAL INSTITUTES OF HEALTH
Allocation of an Additional $500 Million
by Mechanism and by $100 Million Increments
(Dollars in thousands)
Increases Over FY 1991 Request
Includes AIDS

	FY 1991 Pres.Bud. Request	First $100,000 Increment	Second $100,000 Increment	Third $100,000 Increment	Fourth $100,000 Increment	Fifth $100,000 Increment	Total +$500,000
+Other Research.............	---	---	1,355	2,039	713	372	4,479
+Cancer Control.............	---	---	2,115	2,000	---	---	4,115
+AREA Awards................	---	---	2,700	2,500	---	---	5,200
+Construction (MCI).........	---	---	2,000	1,000	---	2,990	5,990
+AIDS.......................	---	---	---	2,500	6,710	9,232	18,442
+New minority initiative (Undergraduate Program)....	---	---	---	250	---	---	250
+Non-AIDS Loan Repaymt Prgm.	---	---	---	1,250	---	---	1,250
+Office of the Director.....	---	---	---	1,000	---	---	1,000
+Research Careers (Incr salary levels).......	---	---	---	---	17,206	---	17,206
+Research Trng Stipends.....	---	---	---	---	---	39,250	39,250
+Extramural Construction (Minority Institutions)....	---	---	---	---	---	15,000	15,000
Subtotal, Increment.........	---	100,000	100,000	100,000	100,000	100,000	500,000
TOTAL.....................	7,929,606	8,029,606	8,129,606	8,229,606	8,329,606	8,429,606	

DHHS - NATIONAL INSTITUTES OF HEALTH

Allocation of an Additional $500 Million
by Institute and by $100 Million Increments
(Dollars in Thousands)
1st $100 Million

	FY 1990 Current Estimate	FY 1991 Request	Noncompeting RPGs (Negotiatns)	Competing RPGs (Negotiatns +349 RPGs)	Research Careers	Research Training	Clinical Trials	Research Centers	R & D Contracts	Intramural/ RMS	SUBTOTAL 1st Increment
NCI......	1,634,294	1,694,059	---	10,467	---	---	1,000	2,000	---	---	13,467
NHLBI....	1,072,335	1,112,502	---	7,922	---	---	---	---	---	---	7,922
NIDR.....	135,744	148,520	65	4,181	---	---	---	---	---	---	4,246
NIDDK....	581,466	605,349	---	4,531	---	---	---	---	---	---	4,531
NINDS....	490,396	512,212	---	8,606	---	---	1,500	---	---	108	10,214
NIAID....	832,960	886,875	---	9,385	---	116	---	---	---	---	9,501
NIGMS....	712,030	745,496	---	6,728	---	---	---	---	---	---	6,728
NICHD....	442,906	461,473	4,818	6,421	---	---	---	1,706	---	---	12,945
NEI......	236,529	247,392	172	1,400	---	---	---	---	---	---	1,572
NIEHS....	229,233	235,792	---	2,000	600	---	---	200	600	705	4,105
NIA......	239,452	248,938	---	12,251	---	---	---	---	---	---	12,251
NIAMS....	168,927	176,080	---	7,527	---	---	---	---	---	---	7,527
NIDCD....	117,582	122,047	154	899	---	---	---	---	---	---	1,053
NCNR.....	33,513	35,127	---	3,938	-	---	---	---	---	---	3,938
NCHGR....	59,538	108,029	---	---	---	---	---	---	---	---	---
NCRR.....	337,105	319,151	---	---	---	---	---	---	---	---	---
FIC......	15,656	16,355	---	---	---	---	---	---	---	---	---
NLM......	85,728	89,916	---	---	---	---	---	---	---	---	---
OD.......	89,916	82,975	---	---	---	---	---	---	---	---	---
B&F......	61,042	88,600	---	---							
TOTAL...	7,576,352	7,929,686	5,209	86,256	600	116	2,500	3,906	600	813	100,000

DHHS - NATIONAL INSTITUTES OF HEALTH

Allocation of an Additional $500 Million
by Institute and by $100 Million Increments
(Dollars in Thousands)
2nd $100 Million

	Noncompeting RPGs (Negotiatns)	Competing RPGs (Negotiatns +152 RPGs)	Research Careers	Research Training	Clinical Trials	Research Centers	R & D Contracts	Intramural/ RMS	FIC/ NLM/ NCRR	Other Research	Cancer Control	AREA Awards	Construction (NCI)	SUBTOTAL 2nd Increment
NCI......	---	10,840	812	685	1,500	2,000	---	---	---	700	2,115	---	2,000	20,652
NHLBI....	---	---	2,711	556	---	8,972	---	1,326	---	142	---	---	---	13,707
NIDR.....	146	769	937	125	---	230	53	---	---	23	---	---	---	2,283
NIDDK....	---	2,000	1,236	99	---	488	216	2,450	---	50	---	---	---	6,539
NINDS....	---	4,021	676	121	1,000	996	161	570	---	32	---	---	---	7,577
NIAID....	---	5,116	600	124	---	---	302	---	---	36	---	---	---	6,178
NIGMS....	2,656	4,010	91	6,224	---	101	80	---	---	64	---	---	---	13,226
NICHD....	---	5,495	---	---	---	---	---	---	---	---	---	---	---	5,495
NEI......	375	1,150	151	170	---	96	95	---	---	171	---	---	---	2,208
NIEHS....	---	1,200	---	353	---	200	447	100	---	---	---	---	---	2,300
NIA......	---	1,955	706	200	---	383	172	---	---	24	---	---	---	3,440
NIAMS....	---	1,551	325	11	---	304	49	---	---	29	---	---	---	2,269
NIDCD....	510	917	---	---	---	---	---	---	---	---	---	---	---	1,427
NCNR.....	69	624	---	209	---	---	---	5	---	3	---	---	---	910
NCHGR....	---	---	---	---	---	---	---	---	---	---	---	---	---	---
NCRR.....	---	---	---	---	---	---	---	---	6,000	---	---	---	---	6,000
FIC......	---	---	---	---	---	---	---	---	1,000	81	---	---	---	1,081
NLM......	---	---	---	---	---	---	---	---	2,000	---	---	---	---	2,000
OD.......	---	---	---	---	---	---	---	---	---	---	---	2,700	---	2,700
B&F......	---	---	---	---	---	---	---	---	---	---	---	---	---	---
TOTAL...	3,756	39,648	8,245	8,885	2,500	13,770	1,575	4,451	9,000	1,355	2,115	2,700	2,000	100,000

DHHS - NATIONAL INSTITUTES OF HEALTH

Allocation of an Additional $500 Million
by Institute and by $100 Million Increments
(Dollars in Thousands)
3rd $100 Million

	Noncompeting RPGs (Negotiatns)	Competing RPGs (Negotiatns +152 RPGs)	Research Careers	Research Training	Clinical Trials	Research Centers	R & D Contracts	Intramural/ RMS/OD	FIC/ NLM/ NCRR	Other Research	Cancer Control	AREA Awards	Constructn (NCI)	AIDS	Minority Initiative Undergrad Program	Non-AIDS Loan Repaymt Program	SUBTOTAL 3rd Increment
NCI......	---	12,143	100	---	2,000	3,000	750	1,500	---	300	2,000	---	2,000	---	---	---	23,793
NHLBI....	1,042	5,482	---	---	801	3,425	1,806	1,008	---	242	---	---	---	---	---	---	13,806
NIDR.....	209	662	---	---	544	395	91	99	---	39	---	---	---	---	---	---	2,039
NIDDK....	638	1,053	---	---	801	2,836	370	1,216	---	86	---	---	---	---	---	---	7,000
NINDS....	578	1,096	---	121	2,000	551	275	108	---	56	---	---	---	---	---	---	4,785
NIAID....	---	4,482	---	400	622	212	517	230	---	62	---	---	---	---	---	---	6,525
NIGMS....	2,247	4,574	---	---	---	172	137	245	---	110	---	---	---	---	---	---	7,485
NICHD....	1,470	---	---	---	2,000	---	---	---	---	---	---	---	---	2,500	---	---	5,970
NEI......	544	1,100	---	---	653	164	163	95	---	294	---	---	---	---	---	---	3,013
NIEHS....	108	1,100	135	---	---	800	643	---	---	---	---	---	---	---	---	---	2,786
NIA......	213	2,074	---	---	575	657	295	148	---	41	---	---	---	---	---	---	4,003
NIAMS....	176	1,421	---	---	270	521	84	72	---	50	---	---	---	---	---	---	2,594
NIDCD....	465	659	---	532	126	---	25	---	---	---	---	---	---	---	---	---	1,807
NCNR.....	388	---	---	---	---	---	---	39	---	5	---	---	---	---	---	---	432
NCHGR....	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
NCRR.....	---	---	---	---	---	---	---	---	7,000	---	---	---	---	---	---	---	7,000
FIC......	---	---	---	---	---	---	---	55	1,000	139	---	---	---	---	---	---	1,194
NLM......	---	---	---	---	---	---	---	---	1,000	---	---	---	---	---	---	---	1,000
OD.......	---	---	---	---	---	---	---	1,000	---	---	---	2,500	---	---	250	1,250	5,000
B&F......	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	-----	------	-----	-----	-----	------	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-------
TOTAL...	8,078	35,846	235	1,053	10,392	12,733	5,156	5,815	9,000	1,424	2,000	2,500	2,000	2,500	250	1,250	100,000

DHHS - NATIONAL INSTITUTES OF HEALTH

Allocation of an Additional $500 Million
by Institute and by $100 Million Increments
(Dollars in Thousands)
4th $100 Million

	Noncompeting RPGs (Negotiatns)	Competing RPGs (Negotiatns +119 RPGs)	Research Careers	Research Training	Clinical Trials	Research Centers	R & D Contracts	Intramural/ RMS	MLM/ NCRR	Other Research	AIDS	Research Careers (Salaries)	SUBTOTAL 4th Increment
NCI......	---	9,650	250	1,000	1,000	---	2,236	2,000	---	550	2,000	1,213	19,899
NHLBI....	---	4,537	---	1,638	596	1,758	2,244	783	---	27	308	4,869	16,760
NIDR.....	237	483	---	---	476	568	60	---	---	4	35	1,659	3,522
NIDDK....	1,649	1,850	---	---	780	1,193	243	750	---	10	40	2,285	8,800
NINDS....	1,494	1,855	675	---	---	457	102	---	---	6	119	2,407	7,115
NIAID....	---	3,911	300	---	611	176	341	817	---	7	2,936	1,020	10,119
NIGMS....	2,532	3,534	---	300	---	142	90	10	---	12	107	163	6,890
NICHD....	---	---	---	---	4,400	---	---	---	---	---	1,000	1,061	6,461
NEI......	709	850	---	---	571	135	107	218	---	33	41	313	2,977
NIEHS....	279	1,075	---	---	---	200	336	680	---	---	96	122	2,788
NIA......	551	1,499	---	---	503	545	195	265	---	5	6	830	4,399
NIAMS....	455	815	---	---	236	431	55	114	---	6	10	558	2,680
NIDCD....	---	---	---	---	108	1,554	---	---	---	---	4	230	1,896
NCNR.....	394	---	---	---	---	---	---	8	---	1	8	163	574
NCHGR....	---	---	---	---	---	---	---	---	---	---	---	177	177
NCRR.....	---	---	---	---	---	---	---	---	3,675	---	---	136	3,811
FIC......	---	---	---	---	---	---	---	---	---	52	---	---	52
NLM......	---	---	---	---	---	---	---	---	1,000	---	---	---	1,000
OD.......	---	---	---	---	---	---	---	---	---	---	---	---	---
B&F......	---	---	---	---	---	---	---	---	---	---	---	---	---
TOTAL...	8,300	30,059	1,225	2,938	9,281	7,159	6,009	5,645	4,675	713	6,710	17,206	100,000

DHHS - NATIONAL INSTITUTES OF HEALTH

Allocation of an Additional $500 Million
by Institute and by $100 Million Increments
(Dollars in Thousands)
5th $100 Million

	Noncompeting RPGs (Negotiatns)	Competing RPGs (Negotiatns +77 RPGs)	Research Training	Research Centers	R & D Contracts	Intramural/ RMS	Other Research	Constructn (NCI)	AIDS	Research Training Stipends	Extramural Constructn (Minority Institutns)	SUBTOTAL 5th Increment	SUBTOTAL Five Increments	TOTAL FY 1991 Revised Estimate
NCI......	---	---	---	---	2,000	2,000	300	2,998	2,000	5,309	---	14,607	92,410	1,706,477
NHLBI....	---	3,922	717	1,086	593	---	---	---	617	6,639	---	13,574	65,651	1,170,153
NIDR.....	149	321	---	202	38	---	---	---	61	847	---	1,618	13,708	154,220
NIDDK....	439	2,099	---	420	121	---	---	---	88	3,984	---	7,151	34,109	639,450
NINDS....	398	1,585	---	282	90	---	---	---	239	2,254	---	4,848	34,599	546,011
NIAID....	---	2,523	610	100	178	---	---	---	5,872	2,719	---	12,002	44,325	931,200
NIGMS....	1,087	2,814	---	88	45	---	---	---	215	8,251	---	12,500	46,029	792,323
NICHD....	---	---	812	1,412	---	900	---	---	---	2,397	---	5,521	38,392	497,085
NEI......	229	687	---	84	56	---	---	---	82	957	---	2,095	11,065	259,257
NIEHS....	74	1,152	---	---	---	---	---	---	---	1,368	---	2,594	14,573	250,305
NIA......	147	1,129	---	336	97	---	---	---	13	1,400	---	3,122	27,223	276,161
NIAMS....	121	690	---	287	20	---	---	---	21	1,061	---	2,200	17,278	183,350
NIDCD....	---	---	---	---	110	648	---	---	8	521	---	1,298	7,277	130,124
NCNR.....	270	---	---	---	---	3	---	---	16	531	---	820	6,674	41,001
NCHGR....	---	---	---	---	---	---	---	---	---	616	---	616	793	108,022
NCRR.....	---	---	---	---	---	---	---	---	---	376	15,000	15,376	32,107	351,338
FIC......	---	---	---	---	---	---	72	---	---	---	---	72	2,399	10,754
NLM......	---	---	---	---	---	---	---	---	---	---	---	---	4,000	93,916
OD.......	---	---	---	---	---	---	---	---	---	---	---	---	7,700	90,675
B&F......	---	---	---	---	---	---	---	---	---	---	---	---	---	80,600
TOTAL...	2,914	16,906	2,139	4,293	3,347	3,551	372	2,998	9,232	39,250	15,000	100,000	500,000	8,429,606

Mr. NATCHER. Dr. Raub, this has been a good hearing. You are an excellent witness. Again, we want to thank you. This starts our budget request for the National Institutes of Health.

Beginning tomorrow, we will start with the institutes. This is something we always look forward to, Dr. Raub.

The committee will now adjourn until 10 o'clock in the morning.

[Questions and answers for the record and the justifications follow:]

RESEARCH PROJECT GRANTS

Mr. Natcher. Was the change in the length of grants a deliberate decision by the previous director in consultation with the Institutes?

Dr. Raub. In order to reduce the burden of the lengthy application process for grant applicants, the previous director made the policy decision to encourage the individual institutes and their national advisory councils to consider longer term awards. In addition, some special mechanisms, both for first-time applicants and for mid-career scientists, were put into place to further encourage this. However, the decision making was decentralized in that it was left to the judgment of each institute and its national advisory council rather than being done on an across-the-board basis.

Mr. Natcher. Will the problem of reduced numbers of new awards correct itself as these longer grants come up for renewal in 1991 and 1992?

Dr. Raub. In addition to longer awards, another significant factor contributing to the reduced numbers of competing grants in recent years is the large increases in the number of competing grants between FY 1984 and FY 1988. The increased number of competing grants, in those earlier years, and the trend towards longer awards resulted in a significant increase in the number of noncompeting research project grants in FYs 1989 and 1990. This larger commitment base, together with the policy decision to support approximately the same total level of grants, had the effect of reducing the number of new awards NIH was able to support.

In FY 1991, this situation begins to correct itself. Reductions in the numbers of competing awards in FY 1989 and 1990 plus the fact that some of the longer grants will be coming up for renewal has resulted in a smaller commitment base in FY 1991. This smaller commitment base will enable NIH to fund a total of 5,095 competing awards, 462 more than in FY 1990.

In FY 1992 and beyond, assuming that the total number of research project grants remains constant, a cyclical pattern will obstain. The number of competing grants will increase to approximately 5,300 to 5,400 for two years, decline to about 4,900 to 5,000 for one year, and then increase again to about 5,300 for another two years. This cycle will continue as long as the total number of research project grants remain constant.

Mr. Natcher. Was each Institute allowed to decide independently on the mix between the number of new awards and the level of downward negotiation?

Dr. Raub. In developing the FY 1991 request, the decision was made to fund the same total number of research project grants. Therefore, each institution was not given the discretion to decide independently on the mix between the number of new awards and the level of downward negotiations. The Institutes were given the discretion to allocate funds between noncompeting and competing research project grants, thus having some impact on the level of downward negotiation between noncompeting and competing grants.

TRAINING

Mr. Natcher. The Academy is recommending that the federal government support 11,670 full-time equivalent training positions in 1991. How does this compare with your budget proposal for 1991?

Dr. Raub. The NIH budget proposal for 1991 is for 12,020 full-time training positions (FTTPs). However, because the Academy's methodology for counting the number of FTTP varies somewhat from NIH the two figures are not comparable. The Academy methodological differences include:

- The Academy used estimated figures for 1987, their baseline year. Their calculation of 9,490 for NIH alone is well below 10,624, the actual number of FTTPs funded by NIH in FY 1987.
- The Academy excluded short-term (three month) research training (T35s) while NIH includes these awards in its estimates calculating them on a four for one basis.

Mr. Natcher. How much money would need to be added to your 1991 request to reach the levels recommended by the Academy?

Dr. Raub. For 1991 the NAS recommends a total increase of 400 trainees over the 1990 level for NIH and ADAMHA. NIH estimates that its share of this increase is 363. Approximately $8.8 million would be required by the NIH to fund this increased number of trainees.

Mr. Natcher. The authorizing legislation for training expires this year. What changes will the Department recommend?

Dr. Raub. No changes are recommended for training in the FY 1991 budget, only a simple reauthorization of the Public Health Service Act, Sec. 487, includes National Research Service Awards.

Mr. Natcher. The Alcohol, Drug Abuse and Mental Health Administration uses a system which attempts to replace each year the same number of scientists who are expected to leave. Does NIH use a similar model?

Dr. Raub. The National Institutes of Health (NIH), when estimating the desired number of National Research Service Award (NRSA) trainees and fellows for future years, considers the number of scientists who are expected to leave research, as does the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA).

Since the National Research Service Award Act of 1974, NIH has relied on recommendations of a Committee of the Institute of Medicine/National Academy of Sciences (IOM/NAS) regarding training needs in the biomedical and behavioral sciences ("Biomedical and Behavioral Research Scientists: Their Training and Supply", IOM/NAS, 1989). The labor market assessment model used by the IOM to estimate the number of new researchers needed to meet future personnel demands includes a demographic/economic component that estimates scientist attrition due to death, retirement, outmigration and inmigration.

However, mere replacement of numbers of scientists who leave biomedical research is not sufficient. A more accurate estimate of need would take into account changes in demand for scientists from industry, government, and other nonacademic sources that draw on the same pool of trainees. The IOM model accounts for these factors. Therefore the estimates of personnel needs in biomedical research used by NIH are based on both the predicted need to replace and the predicted need to compete for personnel resources.

CONSTRUCTION GRANTS

Mr. Natcher. What are your current plans for allocating the $15 million appropriated for construction grants last fall?

Dr. Raub. As a result of sequestration, the $15 million appropriated for construction grants has been reduced to $14.8 million. After an analysis of all of the applicable statutes, the language in the appropriations bill and the construction authorities in three of the institutes, NIH plans to allocate these funds as follows. Two Requests for Applications (RFAs) will be issued. One focuses on a single mouse breeding facility large enough to meet national and international resource needs. The second RFA is for all other construction projects falling within the NIH extramural construction authorities. In addition, because there are a number of applications already in-house and reviewed, with excellent scores, $2 million will be allocated to the NCI for these projects.

Because of the unique significance of the mouse breeding facility problem, it was determined that $10 million would be made available for this project. The awarding of these funds will be subject to peer review, and should the best proposal not be able to justify the full $10 million, NIH would make the award at the appropriate amount and make any residual funds available for the other competition. NIH's intent, however, is to be unequivocal in terms of the importance of the mouse breeding facility and to assure that an adequate sum is available to support it.

For the second RFA, the NIH focus will be in areas that fall within existing construction authorities, including cancer; heart, lung and blood; and eye. Consistent with Congressional intent, NIH has taken a broad interpretation of these authorities and will make every effort to ensure that all possible candidates for funding will compete.

With regard to the $2 million allocated to the NCI for projects already reviewed, it is expected that awards will be negotiated with the top two facilities on the list. Should the entire $2 million not be required, the remaining amount would be made available for competition under the second RFA described above.

Mr. Natcher. What legislative authority are you planning to use in awarding funds for the animal production facility?

Dr. Raub. The award for construction of a mouse production facility will be made either under the authority of the Public Health Service Act, Title IV, Section 413(b)6(A) as amended by Public Law 99-158 (42 USC 285a-2), or under the authority of an appropriation amendment of Public Law 101-190 to authorize a grant award.

Mr. Natcher. Doctor, tell us if NIH was consulted prior to the decision to set aside $10 million for the animal project, and if so, what your recommendation was?

Dr. Raub. NIH was involved with the Office of the Secretary, DHHS in reaching the decision to target $10 million of the $14.8 million available for research facility construction for construction of a mouse production facility. The NIH recommendation called for the mouse facility RFA and its companion solicitation (see above) each to state that $12.8 million ($14.8 million - $2.0 million for cancer centers construction) was available for all applications. After consultation with the Secretary and senior staff, the RFAs were allocated $10.0 million and $2.1 million, respectively to underserve our interpretation of Congressional intent.

Mr. Natcher. What was the range of cost estimates for this project which were presented to NIH at last fall's conference on the situation at Bar Harbor?

Dr. Raub. At the meeting of the Panel on the Production and Supply of Inbred Strains of Mice for Biomedical Research on September 14 and 15, 1989, the Director of the Jackson Laboratory estimated that it will require $25 million to rebuild the facility. Several commercial animal suppliers indicated that a figure below $10 million may be feasible.

Mr. Natcher. How many organizations are likely to submit applications for the animal funds?

Dr. Raub. We expect very few; perhaps only one or two organizations will submit applications in response to the Request for Applications entitled, "Construction of a Mouse Production Facility."

Mr. Natcher. If the peer review system determines that the project can be done for less money, will you shift to other construction needs?

Dr. Raub. If the peer review system determines that less than $10 million is required for construction of a mouse production facility the excess funds will be used for costs justified in applications submitted for the other NIH extramural research facilities construction projects.

GENOME PROJECT

Mr. Natcher. Dr. Raub, this committee asked NIH to submit a long range spending plan for the genome project. The report we received doesn't have the level of detail which we had expected for a project with a potential price tag of $3 billion. Why can't NIH tell us more about how this money will be spent?

Dr. Raub. The National Center for Human Genome Research (NCHGR) has prepared the following preliminary mechanism break for fiscal years 1991 through 1995 representing what would be needed in this time period. This table is based on $200 million per year for the U.S. program, without taking into account the effects of future year inflation, and assuming two-thirds of this amount is allocated to NIH and one-third to the Department of Energy. It should be noted that these estimates reflect the professional judgment of the NCHGR and have not been reviewed by the Administration in comparison with other scientific priorities.

Further, it is difficult to fix a particular budget distribution at this time, in such a rapidly moving field, where relative costs and technology are changing constantly. Flexibility will be essential so that unexpected opportunities can be pursued effectively. I assure you, every effort will be made to complete the project as economically as possible.

Mr. Natcher. Last month several prominent scientists were quoted in a prestigious science journal as being skeptical about the gene mapping project. What is your response to these concerns?

Dr. Raub: As noted in our five year plan, the rapidity with which advances are being made in genomic science dictates that our goals must be re-evaluated often to ensure that they are realistic and are keeping up with the opportunities available. The human genome program has not changed its genetic mapping goal in any substantive way. All along, the genetic map has been seen as playing a dual role in the Human Genome Project. The first is as a tool for the identification and location of genes that can only be recognized by their effects, such as those that are associated with certain diseases. For this purpose, a three to five centimorgan map is generally considered to be of sufficient resolution. The second role is as a tool to help assemble the physical map. Two years ago, a one centimorgan map was considered to be important to help order physically mapped units. Recently, however, physical mapping techniques have improved and it is now believed a two centimorgan genetic map may be adequate for physical mapping.

This refinement in the goal was based on the assessment of recent technical improvements in mapping. In the same way, we intend to frequently reassess and update the goals of the program in the light of technological improvements in order to keep the cost of the effort as low as possible. It would be a mistake to consider each redefinition of the goals as a failure of the program or a delay in finishing it.

INTRAMURAL RESEARCH

Mr. Natcher. How does the average cost of an intramural research project compare to an extramural grant?

National Center for Human Genome Research
Fundings Estimates for FY 1991 through FY 1995
(Dollars in millions)

	FY 1991 Pres. Budget		FY 1992 Estimate		FY 1993 Estimate		FY 1994 Estimate		FY 1995 Estimate	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:										
Noncompeting	117	34.9	151	49.1	127	41.3	114	37.9	106	35.2
Competing	53	17.7	53	17.7	53	17.7	48	16.0	43	14.3
Subtot.,RPGs	170	52.6	204	66.8	180	59.0	162	53.9	149	49.5
Research Centers:										
Spec/comp.	9	35.7	11	43.7	12	47.6	13	51.6	14	55.6
Subtot.,Centers	9	35.7	11	43.7	12	47.6	13	51.6	14	55.6
Other Res.:										
Careers	12	0.9	15	1.0	15	1.1	15	1.1	15	1.1
Other	18	1.8	20	2.0	20	2.0	20	2.0	20	2.0
Subtot.,Other	30	2.6	35	3.0	35	3.1	35	3.1	35	3.1
Total, Res Grants	209	90.9	250	113.5	227	109.7	210	108.6	198	108.2
Training	FTTP									
Individual	75	1.9	100	2.6	150	3.9	175	4.5	175	4.5
Institutional	149	3.2	199	4.2	319	6.7	341	7.2	349	7.4
Total, Training	224	5.1	299	6.8	469	10.6	516	11.7	524	11.9
R&D Contracts	5	8.0		8.0		8.0		8.0		8.2
RM&S		4.0		4.7		4.7		4.7		4.7
Total, NCHGR		108.0		133.0		133.0		133.0		133.0

Note: Table was prepared without taking into account the effects of future year inflation

Dr. Raub. The NIH intramural research projects are not viewed in terms of average costs. We do not have the data available to provide a meaningful comparison.

Mr. Natcher. What controls do you have in place to ensure that your in-house researchers don't duplicate purchases of equipment and other commonly shared items?

Dr. Raub. Within an Institute the purchase of large items of equipment are reviewed by the Office of the Scientific Director to ensure that the equipment is necessary and does not duplicate existing equipment. In general, for major pieces of equipment that are shared, not only among scientists in the same institute, but scientists in other institutes, the Office of the Deputy Director for Intramural Research, NIH, is involved. The Nuclear Magnetic Resonance facility is a case where people from five institutes share the use of these very expensive machines.

In addition, we have a central equipment rental service which takes over surplus instruments and makes them available to anyone on the campus. This has saved the NIH considerable expense.

DIRECTOR'S DISCRETIONARY FUND AND TRANSFER AUTHORITY

Mr. Natcher. The President's Budget includes two proposals intended to give the Director some independent budget authority. How much money would potentially be involved?

Dr. Raub. The two proposals include the Director's Discretionary Fund and the one percent transfer authority for the NIH Director. With regard to the Director's Discretionary Fund, $20 million is requested in the Office of the Director for this proposal. The availability of this fund will allow NIH to be more responsive to emerging research opportunities and health priorities. The transfer authority will enable the Director to transfer up to one percent of the total amount available to all NIH appropriations to high priority activities, as so designated by the Director. Proposed language also provides that no such appropriation shall be increased or decreased by more than one percent by any such transfers. Within the restrictions, we estimate that approximately $40 million could be transferred.

Mr. Natcher. Can you assure this Committee that its priorities would not be the ones which would suffer if the 1 percent transfer authority were approved?

Dr. Raub. We would be mindful of the Committee's priorities if the one percent transfer authority were approved. The amount of money involved would be relatively small, and the Committee would be notified promptly of any such transfer. The authority is intended to provide for unanticipated resource needs and emerging research opportunities. I believe that these needs and opportunities would be considered a priority to this Committee as well as to NIH and that the proposed authority would permit a more rapid response to them.

ANIMAL FACILITIES

Mr. Natcher. Insert in the record at this point a summary of NIH spending on animal facility improvements, both intramural and extramural, over the last five years.

Dr. Raub. The initial phase of the NIH plan for upgrading intramural animal facilities involves constructing new buildings, 6B on the NIH campus and 110A at the NIH Animal Center at Poolesville, Maryland; major renovations in Buildings 10A and 36; and smaller renovations in Buildings 7, 14D, 29A, 30, and 41. A program to renovate or upgrade existing accredited facilities that are reaching the end of their useful life is being initiated in FY 1990, including design of the highest priority projects.

By the end of FY 1990, NIH will have spent $27.7 million for intramural animal facility improvements as follows:

NATIONAL INSTITUTES OF HEALTH
Intramural Animal Facilities
Funding Summary
(Dollars in Thousands)

	Buildings & Facilities, AAALAC	Buildings & Facilities R&I	Operating Funds	Total
1986 Actual	0	$637	$ 362	$ 999
1987 Actual	$ 8,111	0	5,264	13,375
1988 Actual	5,240	0	1,250	6,490
1989 Actual	956	0	1	957
1990 Est.	5,843	0	0	5,843
Total	$20,150	$637	$6,877	$27,664

Obligations for extramural animal facility improvements from FY 1986 to FY 1990 in the appropriation for the National Center for Research Resources Animal Facilities Improvement programs are as follows:

FY 1986 - $ 3,820,000
FY 1987 - 9,848,000
FY 1988 - 11,778,000
FY 1989 - 11,131,000
FY 1990 Est. - 10,931,000

In addition, the National Center for Research Resources has spent approximately $3,000,000 per year on renovations and improvements in the Primate Research Centers.

INDIRECT COSTS

Mr. Natcher. Insert in the record a 10-year table showing average rates and total cost of indirect cost payments.

Dr. Raub. The following table displays the requested information for 1981 through 1991:

STATISTICAL DATA - RESEARCH GRANTS 1/
PERCENTAGE OF INDIRECT COSTS TO TOTAL DOLLARS AWARDED
(Dollars in thousands)

Fiscal Year	Dollars	Indirect Costs Awarded	Percentage
1981	$2,224,138	$655,143	29.5
1982	2,300,534	689,855	30.0
1983	2,584,787	791,580	30.6
1984	2,958,266	921,627	31.2
1985	3,412,923	1,069,707	31.3
1986	3,564,061	1,119,115	31.4
1987	4,188,369	1,311,539	31.3
1988	4,540,758	1,416,716	31.2
1989	4,846,110	1,530,547	31.6
1990 Estimate	5,080,114	1,625,636	32.0
1991 Request	5,603,766	1,793,205	32.0

1/ Actual data from the Indirect Cost Management System (ICMS). Includes research project grants, research centers, research career awards, organ system, clinical education, cooperative clinical education, minority biomedical research support and cancer control grants.

Mr. Natcher. Insert in the record at this point a short description of the Department of Agriculture limit on indirect cost payments with an estimate of the amount which would be saved if a similar system were used at the NIH.

Dr. Raub. For Fiscal Year 1990, Congress has limited indirect cost payments on research grants awarded competitively by the Cooperative State Research Service to 25 percent of total direct costs under each award (H.R. 2883, Section 639).

During Fiscal Year 1989, NIH awarded $3.3 billion in direct costs for research grants. Indirect costs were awarded at a rate of approximately 46.2 percent of direct costs, or $1.5 billion. If for Fiscal Year 1989 NIH had been limited to awarding indirect costs at a rate of 25 percent for all research grants, indirect costs awarded would have been $825 million for a potential savings of $675 million.

OBJECT CLASSIFICATION

Mr. Natcher. Provide a consolidated object classification listing for all NIH accounts for 1989-1991.

Dr. Raub. The following table displays the budget authority by object classification for NIH for fiscal years 1989 to 1991:

CHRONIC FATIGUE SYNDROME

Mr. Natcher. How many extramural grants directly related to chronic fatigue syndrome does the NIH now fund?

Dr. Raub. We are currently funding 3 extramural grants directly related to chronic fatique syndrome.

Mr. Natcher. Is the NIH using a university-affiliated research center approach to Chronic Fatigue Syndrome research?

Dr. Raub. That strategy is not being used in a formal sense. Nevertheless, NIAID has made two awards to Harvard University where investigators from several disciplines are working together on this problem. Moreover, communication among Harvard investigators, NIAID grantees at other universities, and NIAID intramural scientists is excellent.

Mr. Natcher. Who is responsible for coordinating Chronic Fatigue Syndrome research at the NIH?

Dr. Raub. The National Institute of Allergy and Infectious Diseases is taking the lead in this effort. Extramural research is coordinated by Dr. John R. La Montagne, Director, Division of Microbiology and Infectious Diseases, assisted by Dr. Ann Schluederberg, Virology Branch. They work closely with intramural scientist, Dr. Stephen Straus, who collaborates with investigators in several different NIH institutes and with extramural researchers.

DHHS - NATIONAL INSTITUTES OF HEALTH

Budget Authority by Object Classification

(Dollars in thousands)

	1989 1/ Actual	1990 Estimate	1991 Estimate
Personnel compensation:			
Full-time permanent	$248,637	$278,403	$297,229
Other than full-time permanent	75,535	84,261	89,442
Other personnel compensation	14,063	15,184	16,287
Special personal services payments	26,877	25,605	29,765
Total personnel compensation	365,112	403,453	432,723
Personnel benefits	65,511	70,416	75,529
Benefits to former personnel ..	315	422	537
Travel and transportation of persons	15,456	16,781	17,374
Transportation of things	2,773	3,291	3,368
Communications, utilities, and rent	30,259	32,845	33,661
Printing and reproduction	10,020	11,012	11,213
Other services:			
Project contracts	588,846	628,574	644,747
Centrally furnished services	272,563	308,588	331,920
Standard level user's charge	9,848	11,912	12,464
Other	311,621	373,389	406,765
Supplies and materials.........	90,139	94,940	101,188
Equipment	60,204	64,733	67,217
Grants, subsidies, and contributions	5,342,404	5,552,323	5,786,720
Insurance claims & indemnities	1	0	0
Interest	6	3	3
Land and structure	17	0	0
Literature	3,527	3,670	4,257
Total Object Class	7,168,622	7,576,352	7,929,686

1/ Includes $23,858 of no-year extramural construction budget authority appropriated in 1988 which was available for obligation in FY 1989.

CLINICAL CENTER

Mr. Natcher. What is the current situation with turnover and pay for the nurses and allied health workers at the Clinical Center?

Dr. Raub. Through the implementation of many Title 38 authorities, the National Institutes of Health has substantially improved its ability to recruit and retain well-qualified nurses and allied health professionals in increasingly competitive labor markets. Vacancy and turnover rates in the majority of these health care fields have been significantly lowered as a result of Title 38 authorities. This increased staffing stability has improved the morale of both employees and managers, allowing them to direct their efforts toward improved patient care and fuller involvement in research endeavors. The image of the Clinical Center as an employer of health care employees has also improved substantially and, thus, has encouraged greater applicant interest.

In the Clinical Center, the vacancy rate for nurses has decreased from 10 percent in early 1987 to a rate of 7 percent in January 1990. Also, since implementations of the legislation, the turnover rate for nurses has dropped from 25 percent in 1986 to 13 percent in 1989. Improved nurse staffing stability has enabled the Nursing Department to focus more actively on retention efforts, such as education and recognition programs, which have resulted in strengthened employee commitment to NIH. In turn, NIH nurses are presenting a very positive impression of NIH within the nursing community, further facilitating nurse recruitment.

Despite growing labor market shortages of many allied health professionals, NIH has substantially lowered vacancy and turnover rates for the majority of these employees as a result of the implementation of Title 38. In the Clinical Center, all ten allied health occupations that have been under a Title 38 special salary rate for at least six months have lowered vacancy rates, with four occupations reporting no vacancies in January 1990. Eight of these fields have also reduced turnover rates. Managers feel the caliber of their staffs has greatly improved because of better qualified applicants and greater opportunity for managers to devote more time to staff developments and the encouragement of fuller staff participation in research efforts.

INSTITUTIONAL RECIPIENTS

Mr. Natcher. Insert in the record an updated table similar to those previously supplied to the Committee showing total NIH support for the top 25 institutional recipients in 5-year intervals including the most recent year available and including their rank in terms of funding in each year.

Dr. Raub. The following table displays the total NIH support for the top 25 institutional recipients for FY 1989.

CLINICAL TRIALS

Mr. Natcher. How much money is budgeted for clinical trials in 1989, 1990 and 1991?

DHHS-NATIONAL INSTITUTES OF HEALTH

TOP 25 RECIPIENTS OF NIH RESEARCH GRANTS SUPPORT IN FISCAL YEAR 1989

	Institution	Location	Direct Costs	Indirect Costs	Total	Ranking in: 1984	1979	1974
1.	Johns Hopkins University	Baltimore, MD	$88,287	$47,167	$135,454	1st	1st	8th
2.	University of California-SF	San Francisco, CA	95,331	29,723	125,054	2nd	3rd	2nd
3.	University of Washington	Seattle, WA	77,914	31,662	109,576	8th	9th	3rd
4.	Stanford University	Stanford, CA	61,846	38,995	100,841	6th	5th	7th
5.	Yale University	New Haven, CT	60,167	36,414	96,581	4th	6th	6th
6.	Columbia University	New York, NY	52,107	35,247	87,354	7th	7th	10th
7.	University of California-LA	Los Angeles, CA	61,324	24,635	85,959	9th	8th	4th
8.	University of Pennsylvania	Philadelphia, PA	54,125	31,572	85,697	5th	4th	5th
9.	University of Michigan	Ann Arbor, MI	55,197	29,423	84,620	12th	17th	16th
10.	Harvard University	Cambridge, MA	51,068	28,782	79,850	3rd	2nd	1st
11.	Washington University	St. Louis, MO	52,271	27,500	79,771	10th	12th	9th
12.	Duke University	Durham, NC	52,670	22,316	74,986	15th	13th	11th
13.	University of Wisconsin	Madison, WI	52,220	20,487	72,707	13th	10th	13th
14.	University of California-SD	LaJolla, CA	51,657	20,772	72,429	16th	15th	19th
15.	University of Minnesota	Minneapolis, MI	50,905	19,447	70,352	14th	11th	12th
16.	University of North Carolina	Chapel Hill, NC	44,710	18,675	63,385	23rd	n.a.	n.a.
17.	Yeshiva University	New York, NY	36,073	24,911	60,984	11th	14th	15th
18.	University of Rochester	Rochester, NY	39,823	19,274	59,097	21st	n.a.	n.a.
19.	Cornell University	New York, NY	39,007	17,804	56,811	18th	18th	n.a.
20.	University of Chicago	Chicago, IL	35,222	20,197	55,419	17th	20th	n.a.
21.	Brigham & Women's Hospital	Boston, MA	36,508	17,989	54,497	40th	n.a.	n.a.
22.	Baylor College of Medicine	Houston, TX	38,196	15,439	53,635	26th	n.a.	n.a.
23.	University of Alabama	Birmingham, AL	38,490	14,763	53,253	24th	n.a.	n.a.
24.	Mass. Inst. of Technology	Cambridge, MA	33,376	18,080	51,456	19th	19th	18th
25.	Univ. of Southern Calif.	Los Angeles, CA	32,518	17,458	49,976	27th	n.a.	n.a.
			1,291,012	628,732	1,919,744			

n.a. = Not available

Dr. Raub. In FY 1989, $495,511,000 was spent on clinical trials. Estimated funding for FY 1990 is $567,879,000, and for FY 1991, $586,623,000.

Mr. Natcher. What is the projected first year and full cost of all clinical trials currently approved but unfunded, if available?

Dr. Raub. The projected first year cost of all major clinical trials currently approved but unfunded is $256,036,000. The estimated total cost of these trials is $1,415,175,000.

INTRAMURAL RESEARCH

Mr. Natcher. Identify the share of intramural research costs attributed to personnel, equipment and other major expenditure areas.

Dr. Raub. In FY 1991, intramural research costs are distributed as follows:

	Amount	Percent
Personnel	$310,888,000	33.9%
Equipment	49,188,000	5.4
All Other	554,837,000	60.7
(Contractual Services)	(433,416,000)	
(Supplies and Materials	(90,576,000)	
(Other)	(30,845,000)	
Total	$914,913,000	100.0

Mr. Natcher. Does creation of the endowed chairs require point-of-order authorization language?

Dr. Raub. The appropriation language submitted for the creation of the endowed chairs would be subject to point-of-order.

PEDIATRIC AIDS FUNDING

Mr. Natcher. What are your current plans for funding of pediatric AIDS research in 1990 and 1991?

Dr. Raub. The NIH funding for pediatric AIDS in FY 1989 was $55.3 million. It is estimated to be $73.8 million in FY 1990 and $81.6 million in FY 1991, a 10.6 percent increase over FY 1990.

Mr. Natcher. How much of the increase in grant cost is related to pay raises for grant supported personnel? We hear stories of 40-50 percent increases over the last three years.

Dr. Raub. One of the most recent reviews that included a survey of the salaries received by faculty researchers was done by the Office of Inspector General, Office of Audit, DHHS. The Survey Report on the Cost of Research at Colleges and Universities reviewed a small sample of grants and contracts at eight institutions. Based on the actual expenditures for salary and wages for the five years ending December 31, 1988, the study concluded that salaries for faculty researchers increased 34.4% between 1984 and 1988. It should be noted that the costs of biomedical research have been rising faster than the increase in the consumer price index.

NIH responds to rising research costs in three ways. First, we make grant funding decisions based on the recommendations of the scientists who serve on our internal review groups. Second, for fiscal year 1990, as a result of the pay cap on NIH grants, faculty cannot charge a salary to a grant higher than $120,000 per year. Finally, during each grant's non-competing years of support, NIH allows only up to a 4% increase from year to year.

SALARY CAP

Mr. Natcher. How much money is being saved in 1990 and 1991 as a result of the salary cap which was enacted last year?

Dr. Raub. Approximately $10 million will be saved in FY 1990 and FY 1991.

UNAUTHORIZED ACTIVITIES

Mr. Natcher. Would you insert at this point a list of all unauthorized activities at NIH with the 1990 and 1991 budgets for each.

Dr. Raub. Below are a list of the unauthorized activities and the FY 1990 and FY 1991 budgets for each:

	FY 1990	FY 1991
NCI		
Title IV, Part A	$1,552,765,000	$1,582,807,000
Cancer Control	74,944,000	75,459,000
	1,627,709,000	1,658,266,000
NHLBI		
Title IV, Part B	963,661,000	985,526,000
Prevention & Control	82,500,000	82,500,000
	1,046,161,000	1,068,026,000
NRSAs	286,662,000	291,623,000
Medical Library Assistance	12,852,000	13,191,000

DECADE OF THE BRAIN

Mr. Conte. Last year my Decade of the Brain initiative was passed and signed by President Bush. We've been going full speed ahead with the neurology and mental health institutes in developing programs that would harness the tremendous creative energies and translate them into better treatment and cures. NIH has at least 5 institutes involved in some aspect of brain research. What do you think could be done to make the decade of the brain a truly collaborative effort at NIH?

Dr. Raub. The NINDS Advisory Council has appointed a national panel--including members of the voluntary and professional groups involved in the neurosciences--to develop a Decade of the Brain research implementation plan. This effort is specifically directed at identifying the research areas of special opportunity within the mandate of NINDS, and the resources necessary to take advantage of recent and expected progress in neurological research. We agree that the Decade of the Brain also provides a unique opportunity for further collaboration among the many organizations concerned with neuroscience research. NIH is currently participating in a work group convened by the President's Office of Science and Technology Policy (OSTP). The Deputy Director, NINDS is assisting OSTP in convening the group to identify government-wide initiatives for the Decade of the Brain. Other NIH institutes participating include the National Eye Institute, the National Institute on Aging, the National Institute of Child Health and Human Development, and the National Institute on Deafness and Other Communication Disorders. The National Institute of Mental Health, other DHHS agencies and offices, and organizations throughout the Federal Government are already participation or will ~~soon be~~ invited to join the group.

SENIOR BIOMEDICAL RESEARCH SERVICE

Mr. Conte. Recently, I submitted legislation that would create a Senior Biomedical Research Service at NIH. Last year I asked Dr. Wyngaarden how much he thought it would cost to bring NIH salaries to where they ought to be. He said the cost would be around $11.7 million. Could you provide, for the record, an estimate for this year on how much it would cost to bring salaries in line, based on the provisions of my bill?

Dr. Raub. Because of the pay increase in January 1991, the estimate now is $9.4 million.

DIRECTOR'S DISCRETIONARY FUND

Mr. Conte. The budget request includes $20 million for the establishment of a NIH Director's Discretionary fund. How would this discretionary fund be used?

Dr. Raub. The Director's Discretionary Fund would enable NIH to respond more rapidly and effectively to unexpected research needs, emerging priorities and inter-institute research opportunities. In these circumstances, the Director needs the resources to initiate activities across institute lines, without imposing on the independence of the individual institutes.

Mr. Conte. What are some of the priority disease research areas that could have helped by a Director's fund, if it had been available this year?

Dr. Raub. Had the Fund been available for FY 1990, NIH could use it to narrow the range of downward negotiations and award rates for research project grants across the Institutes. The fund could also be used to support a few additional clinical trials.

PEDIATRIC AIDS

Mr. Conte. Last year we identified pediatric AIDS as a high priority area within the discretionary fund. Unfortunately by the time we got out of conference the discretionary fund was gone and no money was available for pediatric AIDS. Doctor, what is NIH doing in pediatric AIDS, and what are the key opportunities that can be made in research? What is known about the maternal transmission factors for AIDS? Why do some infected mothers pass on the virus and some don't?

Dr. Raub. HIV infection in children is the most rapidly growing area of AIDS disease, and the epidemic has hit minority children particularly hard: eighty-nine percent of pediatric AIDS patients are black or Hispanic. The focus for pediatric AIDS research at the National Institutes of Health is in the area of therapeutic intervention. Therapeutic research in pediatric AIDS includes both treatment of children who are already infected with the human immunodeficiency virus (HIV) as well as the treatment of pregnant HIV-infected women to prevent the transmission of the virus from the mother to the child. In addition, other important areas where research is necessary include: 1) the immunological effect of the virus on young children, 2) the early diagnosis of HIV in infants, 3) the clinical manifestations of HIV disease in infants and children, and 4) the mechanism of transmission of HIV from mother to fetus.

The pediatric AIDS research efforts of the National Institutes of Health are centered in three specific Institutes: The National Institute of Allergy and Infectious Disease (NIAID), The National Institute of Child Health and Human Development (NICHD), and the National Cancer Institute (NCI). As I am sure you and the Committee are aware, each of these Institutes brings distinct areas of expertise to this collective effort.

Therapy Research

The recent joining of the clinical trials groups from the NICHD and the NIAID into a single clinical trials entity will enhance the NIH's ability to support the development of treatments for HIV-infected children and measures to prevent the transmission of the virus from HIV-infected women to their children. This expanded clinical trials network will soon offer access to state-of-the-art research to the majority of HIV-infected children and pregnant women in the United States.

The NIH is engaged in a number of basic and applied clinical studies in pediatric AIDS. Clinical research has already demonstrated that the quality and duration of life for HIV-infected infants and children can be improved. Studies conducted by the NIAID and the NCI were pivotal in the recent FDA decision to grant treatment IND status to zidovudine for children three months to 12 years of age who have AIDS or symptoms of HIV infection. This important advance will make zidovudine the first treatment for HIV infection to become widely available for children, furnishing hope of improving or even extending their lives.

NCI's Pediatric Branch is a world leader in the development of new therapies to treat children infected with the AIDS virus. Studies of antiretroviral therapy, for example, has led to a significant improvement in the HIV-associated neurodevelopmental deficits. We have observed that with the use of antiretroviral agents such as AZT (azidothymidine or zidovudine) and ddI (dideoxyinosine), there can be virtual reversals of AIDS dementia in children. For example, in one clinical trial we observed that children with AIDS increased their IQ scores by an average of 15 points after six months of therapy. This was accomplished by dramatic changes in behavior, interactiveness, and regaining lost skills, including speech, walking and resumption of normal childhood activities.

A graphic vignette of an eight year old youngster who had acquired his infection from a blood transfusion during heart surgery in the early 1980's illustrates the effectiveness of AZT in helping children to regain developmental milestones. During the months prior to this child's treatment at the NIH Clinical Center in the summer of 1988, he had regressed in all his cognitive and functional skills. He was sleeping up to 20 hours a day, had dropped out of school and had a loss of more than 30 points in his IQ score compared to testing that had been done before the onset of his illness. His affect had become flat and his mother commented that he wasn't able to express emotions. For example, he seemed unable to cry, even when he seemed to want to. After six months of therapy with the combination of AZT and dideoxycytidine (ddC), his repeat testing showed that his IQ had increased by more than 30 points and he was again alert, interactive -- in almost every way back to normal. He re-entered school last Fall. In addition, improvements in immune function, in appetite, weight, growth velocity and reductions in the size of swollen lymph nodes, liver and spleen have also occurred. However, none of these improvements represent cures; current therapies can only be considered as delaying the progression of the disease.

An NCI priority is the development of new regimens utilizing both AZT and ddI to improve treatment efficacy and to study whether resistant strains of HIV develop with such combinations. Other new leads in treatment include soluble CD4 and dideoxycytosine (ddC) alone and in combination with biologic molecules such as gamma interferon and the colony stimulating factors. Considerable work and research are of critical importance. At the same time, the improvements to date give the hope that future efforts will find more effective and permanent solutions. Researchers now have a variety of promising compounds available to design increasingly effective treatment strategies for pediatric AIDS. Indeed, basic biomedical research has already elucidated considerable insights about the nature of this infection and its consequences in infants and children.

At the NIAID the number of pediatric AIDS clinical trials units receiving funding has increased to 15 in 1988, enabling researchers to begin phase II and III trials in children. A new initiative will be published in the near future that will further expand our efforts to reach HIV-infected children and pregnant women; awards are expected to be made in Fall 1990. The NIAID has also strongly encouraged the units that accrue primarily adults to begin pediatric studies as well. As a result, several have begun these vital studies. Another important component to the expansion of pediatric trials units is the establishment of perinatal centers serving women in at-risk populations. This feature will provide for increased attention given to pregnant HIV-infected women and their children in AIDS clinical trials.

A new NIAID initiative that brings treatment research to community-based clinics and physicians is the Community Programs for Clinical Research on AIDS (CPCRA). The CPCRA broadens research opportunities to HIV-infected women, minorities, and intravenous drug users and the clinicians who care for them.

The use of a comprehensive clinical trials system that couples investigational therapy with advanced care and psychosocial care are also important. Centers piloting novel therapeutic concepts will need to work in concert with those making promising therapies available on a broad geographic basis. Such centers will need to deal with families in which one or both parents are infected with HIV as well as with teenagers who may be without families to support them. Thus, research to elucidate the impact of HIV on the family structure and its dynamics is being conducted to develop methodologies to provide the best comprehensive care possible. Such research needs to be sensitive to the multiple cultures which HIV affects within our society. It is also essential that research be continued and targeted for developing treatment and education programs aimed specifically at adolescents since they appear to provide an important link to the future entry of HIV into the heterosexual community.

Early Diagnosis

To provide appropriate therapeutic treatment, it is vital that we be able to differentiate more quickly infants who are actually infected with HIV from those merely testing positive for HIV antibodies as a result of acquiring the antibodies from the mother. A great deal of the basic AIDS-related research will be applicable to solving this problem. For example, the technique of the polymerase chain reaction (PCR) is being evaluated for this question. In addition to ongoing work supported by the NIH, the NICHD was able to fund six grants in this area in FY 1990.

Immunology

Research must still be expanded into the area of the effect of the virus on the immunological system of young children. Greater understanding of biological markers of progression of infection in children will lead to the development of surrogate markers, that will indicate improvement or deterioration in a child's status. This would have immediate application in clinical trials as we would no longer have to rely solely on clinical outcome (serious illness or death) to judge the efficacy of a certain drug.

Clinical Manifestations

Research aimed at improving the diagnosis, treatment and prevention of the bacterial, viral, parasitic and fungal infections which occur in infants and children is of considerable importance. These studies will require the use of novel combination regimens, paralleling the insights gained from the successful treatment of childhood cancer.

Basic research elucidating the pathogenesis of lymphocytic interstitial pneumonitis (LIP) as well as the severe heart, kidney, liver, nutritional and hematological abnormalities which occur in children is also important. Similarly basic research into the growth and neurodevelopmental deficits that occur in HIV-infected children is of considerable importance to the design of regiments to treat or prevent these complications. It should be underscored that insights gained from any of these investigations would have relevance to adults as well as to children.

Transmission

Analysis of research already conducted, some of which has been published in Lancet, indicate that HIV-infected women transmit the virus to approximately 30 percent of their offspring, with premature babies appearing to be at threefold higher risk than full-term babies. Also of note is the preliminary finding that mothers who transmitted HIV to full-term babies had very low or absent antibodies to one of the HIV proteins, gp120. Mothers of uninfected full-term infants appear to confer immunologic protection against HIV infection to their offspring via a high-affinity antibody to gp120.

A new lead regarding maternal-fetal transmission has emerged from a large study of the natural history of HIV infection in pregnant women and their offspring being carried out in collaboration with the National Institutes of Health and the State University of New York Health Sciences Center. In addition, the NICHD is planning to make several awards this year in the area of research into the role of the placenta in the transmission of HIV from mother to fetus.

Other studies from around the world suggest that certain other factors may be important in determining which mother transmits HIV to her infant. For example, it appears that a mother who has already had one child with HIV infection may be more likely to transmit infection to subsequent children. It also appears possible that women who are more advanced in their HIV disease may be more likely to transmit their infection than women who are in earlier states of the disease.

Many other factors are under study in ongoing projects to examine agents which may facilitate or inhibit the transmission of infection from mother to child. Included in these are the genetic makeup of the mother and baby, the mode of delivery of the baby, certain immunologic and biologic parameters, and infectious cofactors (other infections the mother may have at the time). It is likely that important ongoing projects will provide insight into these issues in the coming years.

Expansion and follow-up of these findings is important because this information has relevance for vaccine development and for potential perinatal immunotherapy. Since only about a third of infants born to infected mothers appear to actually become infected, it is important to find out what maternal, viral or infant factors are involved in the risk for infection. Are there specific strains of the virus that are more likely to be transmitted to the fetus? Does the timing of the infection have an impact on the clinical manifestations which evolve and does this affect the child's prognosis? These and many such questions have a major impact on approaching the development of strategies that might block or prevent the infection of the fetus or infant. For example, if transmission could be blocked by early treatment with a drug like AZT or soluble CD4, does it need to be given early in pregnancy, late in pregnancy or at the time of labor and delivery?

One critically important new approach being pursued at NCI is the effort to interrupt the maternal-fetal transmission of HIV during the intrapartum period (labor and delivery) when much of the transplacental transmission is believed to occur. The Pediatric Branch is studying the toxicity and efficacy of CD4, a molecule which binds to HIV, preventing the virus from infecting human cells in HIV-infected infants and children. Once safety and efficacy have been established in these patients, pregnant HIV-positive mothers will receive intravenous CD4 during the intrapartum period and the newborn will receive CD4 for 24 hours after birth. This trial will serve as a pilot study for a subsequent larger scale study to investigate the efficacy of CD4 as prophylaxis against maternal-fetal transmission. Although some of these questions can be addressed in clinical studies, basic laboratory models, including experimental animal models, will be of considerable importance.

The NIAID is sponsoring several studies using AZT in both newborns and pregnant women to try to block this form of HIV transmission. These studies are now getting underway. We have begun the first clinical trial of AZT in pregnant women, a vital first step toward determining whether zidovudine given during pregnancy can prevent mother-to-baby transmission of HIV.

Several major epidemiologic studies are researching questions of transmission of HIV infection from mother to child. In 1988, NIAID funded the Cohort Studies of Perinatal Transmission of HIV and Related Retroviral Infection to look at the mechanisms and cofactors of perinatal HIV transmission. This multicenter, prospective study is also looking at the effect of pregnancy on the natural history of HIV infection and the natural history of HIV infection in the infants born to HIV-infected women.

Two other studies are also researching these critical issues. The Women and Infants Transmission Study (WITS) is a collaborative, multicenter study at four sites in New York, Chicago, Boston, and Puerto Rico which will recruit approximately 700 infected women. A pilot study phase is currently underway. A second study, Maternal Factors Influencing Perinatal Transmission of HIV (the Army Perinatal study), addresses the natural history of pregnancies in infected and uninfected women with HIV, both drug and nondrug users. This study will be conducted at the University of Medicine and Dentistry of New Jersey, Newark, NJ. A pilot study phase is currently underway.

Studies in basic science are also increasing knowledge of the mother-to-child transmission of HIV. Scientists have developed a mouse model of a retrovirus that produces an AIDS-like disease in small animals. Infected mothers can transmit disease to their offspring during birth and nursing. Drugs are being tested in this model for efficacy against these forms of retroviral transmission. Investigators have also developed a heterosexual transmission model for simian immunodeficiency virus (SIV) infection. This model, used to study potential drugs that may prevent transmission, has already given us insights into heterosexual retroviral transmission.

SEQUESTER

Mr. Conte. With the swinging of the sequester axe last year, NIH lost nearly $97 million. The budget choppers said that there would be minimal impact from the sequester. What is the impact of the sequester on NIH? How many additional research grants went unfunded? How many research slots were lost?

Dr. Raub. In accordance with the Omnibus Budget Reconciliation Act of 1989, NIH sequestered $96.6 million or 1.4 percent of its available appropriations with each budget mechanism reduced approximately 1.4 percent. As a result of the sequester, the competing research project grant mechanism was reduced by $27.3 million, resulting in approximately 100 fewer competing awards. In addition, the noncompeting research project grant category was reduced by $31.7 million. The research training mechanism was reduced by $3.9 million resulting in a reduction of 26 research training positions.

RESEARCH PROJECT GRANTS

Mr. Conte. I am concerned over the award rates for approved new and competing project grants. Only 24 percent of approved grants will be funded this year, and next year will not be any better. Not too long ago we were funding 40 to 50 percent of these grants. All the while the research budget for NIH has been rising at a decent clip.

What are the primary factors causing the decline of the funding rates?

Dr. Raub. There are a number of factors that have contributed to the decline of the award rate. One is an increase in the number of applications approved and eligible for funding. We have been analyzing the trends very carefully and believe that the primary cause of this increase in the number of approved applications is better quality of the applications received and more intense competition. This has resulted in only the very best investigators staying in the competition. Many of our grant applications are now renewal requests or from individuals who have been unsuccessful previously and have used the critique provided in the review process to improve their research proposals and reapply. We also believe there has been an upward shift in the mean quality of applications as the competition becomes more severe and our past investments in both research and training pay off. Another significant factor is the increase in the number of competing grants beginning in 1985. As they convert to noncompeting status, they increase the number of noncompeting grants, thus assuming a larger share of the dollars available. The lengthening of the grant award has also played a part in the decline of the award rate.

Mr. Conte. Isn't part of the problem the increasing length of research grants which has taken up funds available for new grants?

Dr. Raub. Yes, the increase in the length of grant awards has played a part.

Mr. Conte. NIH pushed for longer grants in the Mid-80's to stabilize the grants process--why wasn't the possibility of fewer new grants brought forward?

Dr. Raub. When the NIH Director began to encourage the individual institutes to make longer term awards, the effects of the longer awards on the commitment base in future years were considered. However, it was believed that the benefits derived from reducing the burden of the lengthy application process far outweighed the possibility of fewer new grants. It should be noted that if one could examine the total group of investigators, including both noncompeting and competing, supported under the scenario of longer term awards versus the group that would have been funded under the scenario of shorter grant periods, one would most likely find substantial overlays of the lists. Under longer-term awards, many investigators would receive an additional year or two of noncompeting support instead of having to reapply and receive funding under a competing grant.

Mr. Conte. What is most worrisome is the funding rates at some of the major institutes. The Neurology Institute, the Eye Institute, the Deafness Institute are seeing major declines in the award rates. The Aging Institute might see only a 17 percent rate. Many top notch projects are being shut out. What is NIH doing in the management process to stabilize and improve the funding rates?

Dr. Raub. Many difficult choices were made in the development of the FY 1991 budget. In order to maintain overall balance between the NIH funding mechanisms and provide a few increases to high priority activities, award rates for some institutes have seen some reductions. While award rates are less than optimal, in the context of the total budget request, we believe we can still maintain a strong program. In order to improve these rates, NIH would need to redirect resources from other high priority areas, and we do not believe that such action would be in the best interests of the biomedical research enterprise.

AGENCY FOR HEALTH CARE POLICY AND RESEARCH

Mr. Conte. Last year's reconciliation bill created the new Agency for Health Care Policy and Research. Part of the agency's funding comes out of the one percent set-aside account for PHS. The budget request plans to spend a total of $71 million in set-aside money, about $41 million of which comes from NIH funds appropriated for research grants and contracts. Will NIH be participating in any cooperative projects with the new agency?

Dr. Raub. Section 2611 of the Public Health Service Act authorizes that up to one percent of appropriated funds may be used for program evalaution. Over the past five years, NIH has seen its share of the one percent set-aside increase from $14.5 million in FY 1986, to $30.1 million in FY 1989, to $52.8 million in FY 1990. The increase in FY 1990 is largely due to the creation of the new Agency for Health Care Policy and Research.

One of the new authorities mandated to the agency includes the establishment and support of an information center on health care technologies and health care technology assessment, in cooperation with the National Library of Medicine. The National Center for Nursing Research has issued a Request for Applications (RFA) to study Rural Health in Minority Populations, with the resulting grants funded jointly by the NCNR, the AHCPR, and the Health Services and Resources Administration (HRSA). In addition, discussions are underway between the National Cancer Institute and the AGCPR to study the impact of the Physician's Data Query (PDQ) program on physician behavior.

SET-ASIDE ACCOUNT

Mr. Conte. Does the one-percent tap present a major concern for NIH?

Dr. Raub. The NIH is concerned that its one percent assessment has risen sharply (from $14.5 million in FY 1986 to $52.8 million in FY 1990), as noted above, particularly as advance notice is rarely received when large increases are anticipated. For instance, for each $10 million NIH is tapped, we are unable to fund approximately 50 competing research project grants.

CONFLICT OF INTEREST

Mr. Conte. Doctor Raub, last fall NIH proposed guidelines on preventing financial conflict of interest situations between NIH and the outside biomedical research community. Secretary Sullivan suddenly withdrew the guidelines just before the new year. At the time he said that he was instructing NIH to come up with further options to address the conflict of interest issue. Where do things stand in regards to potential conflict of interest proposals?

Dr. Raub. We are in the final stages of completing an evaluation of the 751 comments that we received in response to our Request for Comment on Proposed Guidelines for Policies on Conflict of Interest that was published in the NIH Guide for Grants and Contracts in September, 1989. The many provocative and stimulating ideas among the comments received reflect the community's interest in this controversial topic. Thus, we believe that a careful analysis of those comments will serve as a guide in determining what the next appropriate steps should be. As Secretary Sullivan has indicated, policy changes with respect to conflict of interest will follow the formal rulemaking procedure, which includes publication in the Federal Register and a period of time during which the public can provide comments.

POLYMERASE CHAIN REACTION

Mr. Conte. Doctor, I am very excited to hear of the development of the Polymerase Chain Reaction (PCR). I understand that it is now one of the most powerful tools of biomedical research, and its applications are almost limitless. A new test for Lyme disease was developed with this process. Science magazine called a key enzyme used in PCR as the 1989 Molecule of the Year.

What are some of the potential uses of PCR in biomedical research?

Dr. Raub. The Polymerase Chain Reaction (PCR) procedure serves to effectively "amplify" small amounts of genetic material to levels useful for research and diagnostic purposes. It was developed in 1985. Since that time, as noted in Science, it has grown into "an increasingly powerful, versatile, and useful technique." Applications to date include the diagnosis of genetic diseases, such as sickle cell anemia; the detection of hard to culture infectious agents, such as the one responsible for Lyme disease; and the diagnosis of certain cancers. It has even been used in attempts to identify missing persons, and to determine paternity as well as in some criminal investigations.

According to Dr. Kary Mullis of the Cetus Corporation, the scientist who developed PCR, over 1,000 reports of its use for different scientific purposes have been published to date. Experts believe that, in the future, PCR is likely to replace current laboratory techniques being used for gene sequencing, and its use can be expected to accelerate the pace of progress in the field of molecular genetics generally.

AIR QUALITY STUDY

Mr. Conte. There are allegations that a Harvard professor hid mistakes involving the "Six Cities" air-quality study, a long-running and important project started 15 years ago. There is a strong concern that any serious, uncorrected errors could affect national ambient air quality standards. What is the current status of that investigation?

Dr. Raub. The Office of Scientific Integrity is conducting an inquiry into this matter. The inquiry is nearing completion. The objective is to determine whether or not an investigation is warranted.

CHILD HEALTH AND NEUROSCIENCES BUILDING

Mr. Conte. What is the current status on the construction of the Child Health and Neurosciences building?

Dr. Raub. Final design of the Child Health and Neurosciences Building (49) began in November 1988. Construction of the foundation and site utilities began in July 1989 and was completed in January 1990. The contract for the building superstructure was awarded in January 1990, and we plan to begin construction of the building shell and major mechanical and electrical systems in July 1990.

Mr. Conte. How much is necessary in FY 1991 to complete the next phase of the building?

Dr. Raub. If funding were available in FY 1991, $35.0 million would be required to complete the entire Child Health and Neurosciences Facilities program. If funding were not available until FY 1992, $38.5 million would be required to complete the program. The program includes the construction of Building 49, expansion of Building 6B, a small tower addition to Building 30, infrastructure support facilities, and a multilevel parking structure.

Mr. Conte. When do you anticipate completion?

Dr. Raub. With funding provided in FY 1991, it is estimated that occupancy of Building 49 could occur in late 1992. If funding were not available until FY 1992, occupancy would not occur until late 1993.

HUMAN GENOME PROJECT

Mr. Obey. In Congress one can see what our priorities are based on how much we spend on them, and I assume that is true in the biomedical field. The NIH has decided that the Human Genome project is of high priority. I am very concerned with the ethical and legal questions that this project raises. While I don't know what the right amount is to be spending on defining the major ethical issues and developing policy options to address them, I do know that given the expectations this project has raised for everyone with a genetic disease, cancer, or a chronic condition, and the privacy legal implications this information could uncover, I hope that you will designate adequate resources to address these issues.

I understand that in general approximately 3 percent of the Human Genome budget will be set aside to examine the ethical and legal issues, is that true? How much money have you set aside in 1990 and in 1991?

Dr. Raub: The National Center for Human Genome Research (NCHGR) estimates spending 3 percent, approximately $1,786,000 in FY 1990 and $3,241,000 in FY 1991, of their budget to support conferences, scholarly research and public education through various media. The NCHGR has established a Working Group on Ethical, Legal and Social Issues which has developed a comprehensive program plan for this area and provides guidance about the types of issues we should be addressing. In addition, NCHGR has appointed an expert in the area of bioethics to administer this program. This individual is knowledgeable about these types of issues and knows the community.

The NCHGR issued its first program announcement in March 1989 and the second in February 1990. The response from the community, as determined by the number of applications submitted in response to these announcements, has been very promising.

Mr. Obey. Given the current financial constraints at NIH, limited overall increase in funding for competitive grants and given that the nature of the Human Genome project has changed, it no longer is a well-defined project of sequencing genes from A-Z, is it necessary to be on a fast track with a major financial commitment to this initiative? Would it be wiser to tackle the sequencing project over a longer period of time allowing other basic research projects to be funded?

Dr. Raub: To obtain detailed chromosomal maps and ultimately the complete sequence of the 3 billion base pairs in human DNA has always been, and is still, the goal of the Human Genome Project. In that sense, the nature of the project has not really changed. However, since it was first proposed in 1985, much study and discussion has refined and focussed our mission. Today, leaders in the American scientific community, and indeed across the world, recognize the economy of investment in human genome science. In several separate reports on the technical feasibility and scientific merit of the human genome project, expert panels concluded that current technology provides us with a strong foundation from which to begin mapping and sequencing the human genome, at a recommended cost for the United States of $200 million per year, for 15 years.

Funds for the first three years of operation have been well below $200 million for the combined NIH and DOE programs. Monies allocated to the genome project thus far have been "start-up" funds and we are just beginning to set up the teams of researchers needed to do the job. We have asked for an 80 percent increase over last year's budget so that we may reach the level needed to achieve our goals. The notion of the Human Genome Project is now gaining tremendous momentum in the scientific community as inspired imaginations begin to ponder new ways to approach mapping and sequencing, as well as to muse on a multitude of uses for the finished product. To best exploit the momentum generated thus far, we believe it necessary to reach the recommended levels as quickly as possible.

RESEARCH PROJECT GRANTS

Mr. Obey. What percent of our research dollars are spent on prevention and are these grants more common in the extramural or intramural arena?

Dr. Raub. Approximately 25 percent of NIH research grant and contract dollars are spent on prevention research, and these dollars are overwhelmingly spent in the extramural area.

Mr. Obey. What percent of NIH dollars are being spent on "half way technology as opposed to basic science?

Dr. Raub. Assuming the phrase "half-way technology" refers to Lewis Thomas' statement referring to the iron-lung as such a technology on the way to developing a polio vaccine, then probably less than 10 percent of NIH dollars are being spent on half-way technology as opposed to basic science.

Mr. Obey. Over the last ten years, have we been funding more grants in the area of prevention?

Dr. Raub. Yes; at a minimum of 5 to 10 percent more than a decade ago.

Mr. Obey. On average, are the costs of prevention or basic science research grants higher or lower compared to grants in the clinical research area?

Dr. Raub. On average, costs for prevention research, or basic research relevant to prevention, are considerably lower than are grants in the clinical research area.

Mr. Obey. If one looks at the last ten years of competitive research grants awarded at the NIH, one notices some trends that I think should be highlighted.

Since 1987, 27 percent of the total grants at NIH were, or will be as the case is for 1991, awarded competitively while 32 percent of NIH's grants were awarded during the five year period prior to 1987 (1982 to 1986).

There were 590 fewer grants awarded on a competitive basis in the last five years compared to the previous five year period (1982 to 1986).

The trend in total grant dollars awarded, if the projections for 1990 and 1991 are correct, shows that since 1987, total dollars have increased by 28 percent. However, the projections for dollars available for competing grants has actually, or is projected to decrease by 6 percent during this same time period.

COST OF AWARDS

	1991 (Dollars in Thousands)	1987	Difference
Competing	$1,058,514	$1,129,836	<71,322>
Total	$4,424,775	$3,463,578	961,197

What mechanism exist to ensure that the indirect costs associated with grants to NIH are reasonable? Should there be a cap on the total amount of indirect costs NIH should not exceed?

Dr. Raub. Indirect costs proposals of most colleges and universities and other grantee organizations are submitted to indirect costs specialists of the Department of Health and Human Services for review. These proposals are reviewed for allowability and reasonableness of costs with the applied negotiated rates achieving significant reductions from what was actually proposed.

We do not believe that there should be an arbitrary limitation on the amount of indirect costs awarded under a research project grant.

Indirect costs support important resources at the institution where the research is conducted, such as, facilities, utilities, animal care, and the library. It is important that the government help support these costs.

EXTRAMURAL CONSTRUCTION

Mr. Obey. Dr. Raub, I noticed that the NIH has issued a request for applications for construction of mouse breeding facilities. I want to commend you and Dr. Sullivan for your considerable efforts to restore the much needed supply of specialized research mice. Are there funds available to restore this important resource?

Dr. Raub. Ten million dollars are available for construction of a mouse production facility. Up to 75 percent of the allowable costs of a construction project may be requested from the National Institutes of Health, not to exceed $10 million. Estimates ranging from $10 million to $25 million have been given as the cost of constructing a facility adequate for the production of specialized research mice.

DIAGNOSTIC RADIOLOGY LABORATORY

Mr. Obey. Dr. Raub, last year Congress raised some concerns that NIH does not have a central laboratory to support imaging research. To correct this problem, Congress earmarked $2 million to help establish an intramural research program in diagnostic radiology. As I read your February 16 letter to me, I was troubled to see that instead of setting up a discrete intramural research program, your plans are to create a "research training program." Why did you choose to ignore specific language in both committee reports and the conference report?

Dr. Raub. Building an intramural program in diagnostic imaging research is a multi-step process. NIH is now in the early stages of developing a program that will realize the intent of the committee and conference language. This will be a multi-year effort that includes training radiology fellows in the research process and gradually creating an intramural laboratory research program that builds upon NIH's areas of strength in imaging and computing technology.

In deciding how to implement the report and conference language, I consulted on several occasions with members of the Conjoint Committee and with others expert in the field. There was general agreement that the first step should be establishment of a research training program to bring 3 or 4 research fellows yearly to the NIH. Because diagnostic radiology has historically been a primarily clinical field, there is not a large cadre of radiologists trained to conduct basic research. Therefore, the first step in developing an intramural research program is to expand the numbers of research radiologists. In support of this general strategy, the Conjoint Committee offered to share the recruitment and salary costs for a cohort of 3 to 5 radiology fellows to be recruited annually for a two-year fellowship.

NIH is currently recruiting for a Director of the Radiology Research Program. The Director will organize the research training program and will also begin to develop a laboratory research program in his or her area of specialty interest. In addition, we are procuring a Nuclear Magnetic Resonance machine for the diagnostic imaging research program. NMR is the imaging modality of greatest current interest to the radiology community, and we expect that the first cadre of radiology research fellows will heavily utilize the new magnet and supporting equipment.

In summary, within a 2 to 5 year time-frame, the Committee can expect to see the evolution within the intramural NIH of a full-fledged radiology research program. The essential first steps, however, are to build up the numbers of research radiologists and to carefully develop a program of basic science research in radiology.

SENIOR SCIENTISTS

Mr. Roybal. We are experiencing a serious problem in recruiting and retaining senior scientists. What would be a fair pay package that would attract and retain senior scientists and directors of the various Institutes? How would this package compare with what is being offered in the private sector?

Dr. Raub. To enable the NIH to better recruit and maintain a strong cadre of senior scientists, pay should be more competitive with the salaries offered in research intensive universities. According to the latest data from the Association of American Medical Colleges, the median salary of physician-chairmen of clinical departments in U.S. medical schools is almost twice what the NIH is able to pay its senior physician-scientists. Salaries for senior scientists holding M.D., Ph.D., and other doctoral level degrees could be fixed at rates that would make the NIH more attractive to outside applicants, and would stem the exodus of senior scientists who leave to accept more lucrative positions in the private sector.

Mr. Roybal. How many senior scientist positions are presently vacant at the NIH? Please provide a list of the vacant positions.

Dr. Raub. Currently there are 92 vacant positions that have been certified as being at the Senior Executive Service level. A listing of these positions follows:

Senior Executive Service Vacancies at NIH

ICD	Position Title
OD	Director, National Institutes of Health
OD	Senior Advisor to the Deputy Director for Science
OD	Associate Director for Disease Prevention
OD	Deputy Director for Extramural Research
OD	Director, Division of Planning and Evaluation, Office of Science Policy and Legislation
NCRR	Deputy Director, National Center for Research Resources
NCRR	Director, Division of Intramural Research Resources
NCRR	Director, Division of Extramural Research Resources
NCI	Associate Director, International Affairs
NCI	Associate Director, Extramural Research Program, Division of Cancer Biology and Diagnosis
NCI	Deputy Director, Division of Cancer Etiology
NCI	Associate Director, Chemical and Physical Carcinogenesis Program, Division of Cancer Etiology
NCI	Associate Director, Centers and Community Oncology Program, Division of Cancer Prevention and Control
NCI	Associate Director, Cancer Prevention Research Program, Division of Cancer Prevention and Control
NCI	Deputy Director, Division of Extramural Activities
NCI	Deputy Director, Division of Cancer Treatment

ICD	Position Title
NCI	Associate Director, Cancer Control Science Program, Division of Cancer Prevention and Control
NEI	Deputy Associate Director, Biometry and Epidemiology Program
NHLBI	Director, Office of Prevention, Education, and Control
NIA	Associate Director, Epidemiology, Demography and Biometry Program
NIAID	Deputy Director, Division of Acquired Immunodeficiency Syndrome
NIAMS	Deputy Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	Deputy Director, National Institute of Child Health and Human Development
NICHD	Associate Director for Scientific Review
NIDDK	Deputy Director, Division of Digestive Diseases and Nutrition
NIDR	Director, Epidemiology and Oral Disease Prevention Program
NIDR	Deputy Director, Epidemiology and Oral Disease Prevention Program
NIDR	Chief, Disease Prevention and Health Promotion Branch, Epidemiology and Oral Disease Prevention Program
NIDR	Chief, Analytical Studies Branch, Epidemiology and Oral Disease Prevention Program
NIEHS	Deputy Director, National Institute of Environmental Health Sciences
NIGMS	Director, Biophysics and Physiological Sciences Program
NLM	Associate Director for Extramural Programs
NLM	Director, National Center for Biotechnology Information
NIDCD	Deputy Director, National Institute on Deafness and Other Communication Disorders
NIDCD	Director, Division of Intramural Research
NIDCD	Director, Division of Extramural Activities
NIDCD	Director, Division of Communication Sciences and Disorders
CC	Associate Chief, Positron Emission Tomography and Radiochemistry
NCRR	Head, Magnetic Resonance Imaging Group, Biomedical Engineering and Instrumentation Branch
NCRR	Chief, Chemical Engineering Section, Biomedical Engineering and Instrumentation Branch

ICD	Position
NCI	Chief, Protein Chemistry Section, Laboratory of Biochemistry, Division of Intramural Research, Division of Cancer Biology and Diagnosis
NCI	Chief, Gene Regulation Section, Laboratory of Molecular Biology, Intramural Research Program, Division of Cancer Biology and Diagnosis
NCI	Chief, Surgical Pathology and Postmortem Section, Laboratory of Pathology, Intramural Research Program, Division of Cancer Biology and Diagnosis
NCI	Chief, Laboratory of Mathematical Biology, Intramural Research Program, Division of Cancer Biology and Diagnosis
NCI	Chief, Laboratory of Cell Biology,Intramural Research Program, Division of Cancer Biology and Diagnosis
NCI	Chief, Laboratory of Molecular Virology, Intramural Research Program, Division of Cancer Etiology
NCI	Chief, Laboratory of Molecular Oncology, Division of Cancer Etiology
NCI	Chief, Laboratory of Experimental Carcinogenesis, Division of Cancer Etiology
NCI	Chief, Biometry Branch, Epidemiology and Biometry Program, Division of Cancer Prevention and Control
NEI	Chief, Laboratory of Ophthalmic Pathology, Intramural Research Program
NHLBI	Chief, Laboratory of Cell Biology, Division of Intramural Research
NIA	Chief, Laboratory of Molecular Genetics, Intramural Research Program
NIA	Chief, Laboratory of Cellular and Neurobiology, Intramural Research Program
NIAID	Head, Epidemiology Section, Laboratory of Infectious Diseases,Division of Intramural Research
NIAID	Head, Experimental Pathology Section, Laboratory of Immunology, Intramural Research Program
NICHD	Chief, Contraceptive Development Branch, Center for Population Research
NICHD	Chief, Reproductive Sciences Branch, Center for Population Research
NICHD	Chief, Mental Retardation and Developmental Disabilities Branch, Center for Research for Mothers and Children
NICHD	Chief, Laboratory of Molecular Genetics
NICHD	Chief, Section on Reproductive Endocrinology, Developmental Endocrinology Branch, Intramural Research Program
NICHD	Chief, Section on Molecular Regulation, Laboratory of Molecular Genetics, Intramural Research Program
NICHD	Chief, Section on Macromolecular Analysis, Laboratory of Theoretical and Physical Biology
NICHD	Chief, Laboratory of Neurochemistry and Neuroimmunology, Intramural Research Program

ICD	Position
NICHD	Chief, Section on Child and Family Research, Laboratory of Comparative Ethology, Intramural Research Program
NIDDK	Chief, Phoenix Epidemiology and Chemical Research Branch
NIDDK	Senior Chemist, Endocrine Biochemistry Section, Clinical Endocrinology Branch, Division of Intramural Research
NIDR	Deputy Director, Intramural Research Program
NIDR	Chief, Diagnostic Systems Branch, Intramural Research Program
NIDR	Chief, Laboratory of Cellular Development and Oncology
NIDR	Chief, Laboratory of Developmental Biology and Anomalies, Intramural Research Program
NIEHS	Chief, Laboratory of Cellular and Molecular Pharmacology, Division of Intramural Research
NIEHS	Chief, Laboratory of Molecular Carcinogenesis, Division of Intramural Research
NIEHS	Chief, Laboratory of Reproductive and Developmental Toxicology, Division of Intramural Research
NIEHS	Chief, Laboratory of Molecular and Integrative Neurosciences, Division of Intramural Research
NIEHS	Chief, Laboratory of Cellular and Molecular Pharmacology, Division of Intramural Research
NIEHS	Chief, Laboratory of Molecular Genetics, Division of Intramural Research
NIEHS	Chief, Laboratory of Molecular Biophysics, Division of Intramural Research
NIEHS	Chief, Chemical Pathology Branch, Division of Toxicology Research and Testing
NIEHS	Chief, Experimental Pathology Group, Chemical Pathology Branch, Division of Toxicology Research and Testing
NIEHS	Chief, Cellular and Genetic Toxicology Branch, Division of Toxicology Research and Testing
NIEHS	Chief, Systems Toxicology Branch, Division of Toxicology Research and Testing
NIEHS	Head, Statistics Section, Statistics and Biomathematics Branch, Division of Biometry and Risk Assessment
NINDS	Chief, Infectious Diseases Branch, Intramural Research Program
NINDS	Chief, Laboratory of Neural Regeneration and Implantation, Intramural Research Program
NINDS	Chief, Laboratory of Biophysics, Intramural Research Program
NINDS	Chief, Neuronal Interactions Section, Laboratory of Neurophysiology, Intramural Research Program
NINDS	Chief, Laboratory of Molecular Genetics, Intramural Research Program
NINDS	Chief, Brain Structural Plasticity Section, Laboratory of Neurobiology, Division of Intramural Research
NINDS	Chief, Myelin and Brain Development Section, Laboratory of Molecular and Cellular Neurobiology
NINDS	Chief, Laboratory of Viral and Molecular Pathogenesis, Basic Neorosciences Program

ICD	Position
NINDS	Chief, Medical Neurology Branch
NINDS	Chief, Neuroepidemiology Branch

AIDS--MANAGEABLE, CHRONIC CONDITION

Mr. Roybal. There has been much talk in the press about AIDS becoming a manageable, chronic condition. What is your assessment of this trend? Will accomplishing this goal require greater research and success in treating the opportunistic infections to which people with HIV are usually susceptible?

Dr. Raub. As new drugs are brought from our clinical trials to the clinics and physicians who care for AIDS patients, the potential grows for these patients to lead longer lives with a higher quality of life. We have already seen evidence that death rates from AIDS are diminishing due to the effect of treatment. These trends are very promising and raise hope that HIV infection will be a manageable condition for people infected with the virus.

The treatment of opportunistic infections associated with HIV disease is an extremely important area affecting longevity and quality of life. More promising drugs and drug combinations to treat AIDS-related opportunistic infections are being tested than ever before in NIAID-supported clinical trials. This research is producing new therapies that are extending the lifespans and improving the quality of life for people with AIDS. For example, the recent FDA approval of aerosolized pentamidine represents a promising means of preventing deadly PCP infections in some HIV-infected people. The recent FDA approval of the drug ganciclovir also was a major achievement in AIDS therapeutics this year. Ganciclovir is used to prevent blindness in patients who have cytomegalovirus retinitis, an opportunistic disease that destroys the vision of affected patients. This important advance should have a significant impact on the quality of life of HIV-infected people affected by this disease.

OPPORTUNISTIC INFECTIONS

Mr. Roybal. Is there the same level of interest in researching and studying the opportunistic infections among the pharmaceutical companies and the research community as there is for examining treatments for HIV infection itself?

Dr. Raub. From our perspective, it appears that the pharmaceutical companies are less interested in developing drugs for the AIDS-related opportunistic infections (OIs) than for HIV infection itself. It is possible that this situation has arisen because the pharmaceutical industry does not perceive an adequate incentive for developing drugs for the OIs, each of which affects a subset of AIDS patients. Thus, the patient population for these diseases is much smaller than that targeted for primary HIV infection therapies. Some pathogens affect very small percentages of patients, such as toxoplasmosis, which is seen in about five percent of AIDS patients.

Mr. Roybal. What is being done to assure that OIs get the same level of attention?

Dr. Raub. One of the major goals of the NIH is to stimulate research to discover and develop therapeutic agents for treating opportunistic infections (OIs). These diseases are the major causes of illness and death in AIDS patients and contribute significantly to the medical costs of treating HIV-infected people. HIV-infected patients are susceptible to a wide range of protozoal, fungal, viral, and bacterial infections, whose management is difficult and complicated because: (a) patients are often affected simultaneously by several opportunistic infections, (b) the pathogens may develop resistance to conventional therapies, and (c) AIDS patients are more susceptible to drug-related toxic reactions. Further, most currently available therapies against the opportunistic infections in AIDS patients either have limited efficacy or potentially serious side effects.

Because of the need to intensify research efforts to understand and control these organisms, we have begun a comprehensive, integrated effort to increase research in the OIs. The NIAID coordinated OI program expects to make awards in June 1990. The program encompasses: (1) the National Cooperative Drug Discovery Group (NCDDG)-OI effort, (2) basic investigator-initiated research grants, (3) contracts for screening agents to treat opportunistic infections, (4) animal model contracts to analyze the efficacy and toxicity of single and combination therapies, and (5) resources necessary for the pre-clinical development of therapies for OIs.

This vital new initiative will augment ongoing work, which has already produced results. For example, our screening program results in the screening of hundreds of compounds a year for activity against many of the key opportunistic organisms affecting AIDS patients. These studies have led to the identification of promising drugs, such as the combination of clindamycin and primaquine as treatment and prophylaxis for PCP, now in clinical trial.

In clinical studies, NIAID currently supports a wide range of ACTG-sponsored clinical trials for several of the opportunistic infections that affect AIDS patients. This research is producing new therapies that are extending the lifespans and improving the quality of life for people with AIDS.

Mr. Roybal. What level of funding would be needed to conduct full-scale clinical trials into opportunistic infections?

Dr. Raub. NIAID presently conducts or has planned as high-priority research a wide range of clinical trials for several of the opportunistic infections that affect AIDS patients. This research is producing new therapies that are extending the lifespans and improving the quality of life for people with AIDS. The recent FDA approval of aerosolized pentamidine represents a promising means of preventing deadly PCP infections in some HIV-infected people. Two ongoing studies are geared toward identifying the best preventive therapy for PCP infection, by evaluating the effectiveness of aerosolized pentamidine and other drugs, such as trimethoprim-sulfamethoxazole (trade name Bactrim), in preventing PCP recurrence.

Ongoing and planned clinical trials will assess the value of a number of therapies for active PCP infection. These studies range from trials in people who have mild to moderate disease to studies in those who are very ill with severe PCP. We are evaluating clindamycin and primaquine for mild to moderate PCP. For more severe disease, researchers are studying the efficacy of trimetrexate, which appears to cause fewer side effects than standard therapy. Trimetrexate may alleviate the problem of adverse drug affects that often require physicians to withdraw patients prematurely from life-saving therapy.

NIAID is also about to initiate studies for diseases produced by a variety of less commonly seen infectious organisms, including cryptosporidium, herpes viruses, and candida albicans. Together with the drug company Pfizer, we ~~have~~ conducted a study of a major new treatment for cryptococcyl meningitis. In this clinical trial, the drug fluconazole appeared to be far better tolerated than the traditional therapy, amphotericin. The issue in other diseases at this time is whether the research options are sufficiently important to merit clinical trials. An ongoing process of prioritization is addressing this issue. Within the resources available, however, we believe the answer is no.

The recent FDA approval of the drug ganciclovir was a major achievement in AIDS therapeutics this year. Ganciclovir is used to prevent blindness in patients who have cytomegalovirus retinitis, an opportunistic disease that destroys the vision of affected patients. This important advance should have a significant impact on the quality of life of HIV-infected people affected by this disease. The drug foscarnet also looks highly promising as a therapy for cytomegalovirus retinitis. Because recent studies showed the drug to be very safe, it is hoped that patients may be able to tolerate it for extended periods of time. This advantage would obviate problems with ganciclovir -- its toxicity and restriction that it cannot be taken together with AZT.

Scientists now possess an arsenal of weapons to fight many of the serious opportunistic infections that afflict people with AIDS. This broadened base of treatment options presents an exciting new research challenge. Researchers can, for the first time, compare the benefit of several drugs to determine the optimal treatment for several opportunistic infections. These important studies should provide physicians with the information they need to provide the best possible treatments for AIDS patients.

DRUG DEVELOPMENT

Mr. Roybal. Preclinical drug development for anti-retrovirals is occurring at NCI. The equivalent system for opportunistic infections is being developed at NIAID. Why have the two been divided--is there no overlap in technology?

Dr. Raub. In FY 1989, an agreement was reached between the National Cancer Institute (NCI) and the National Institute of

Allergy and Infectious Diseases (NIAID) dividing responsibilities for drug development. This agreement was based on exploiting the expertise, resources and interests existing in each Institute and ensuring that no overlap would arise. As a result of this agreement, NIAID was charged with the responsibility for the discovery and preclinical development of therapies for opportunistic infections associated with AIDS. For anti-retrovirals, the work was divided as follows: NIAID would sponsor studies in targeted drug discovery, while NCI would direct the intramural AIDS Drug Screen Program and the subsequent preclinical development of drugs discovered in the drug screen.

Historically, the National Cancer Institute has had a preclinical drug development program for anticancer agents, which includes the capacity to identify new drugs, and the ability to conduct comprehensive preclinical drug development for up to three cancer compounds per year. When the identification and development of anti-HIV drugs became a priority several years ago, the NCI undertook this commitment because the necessary scientific experience and drug development program was already in place. The first step was to develop an assay which accurately screens large numbers of compounds for activity against HIV. The resulting screen can now handle up to ten thousand compounds per year and has successfully identified a number of unique classes of agents with _in vitro_ anti-HIV activity. A few of the drugs with anti-HIV activity identified and undergoing development at the NCI include ddI, ddC, FddC and FddI. The NCI also has an extensive acquisition program for natural as well as synthetic products and has developed _in vitro_ mechanistically directed assays, and in vivo assays to further characterize the new anti-HIV drugs.

The core of the NIAID anti-retroviral drug discovery effort is a network of extramural collaborative groups, the National Cooperative Drug Discovery Groups (NCDDGs), which bring together expertise from industry, academia, and government. These Groups sponsor a wide range of projects, including studies of the molecular biology of various organisms involved in HIV infection, the development of unique cell culture assays, the development of animal models for drug development studies, the discovery of new lead therapeutics, the rational design of new compounds, studies of structural biology (such as x-ray crystallography), studies of protein structure, and research of the biophysical properties of HIV and cell proteins. These efforts are already expanding the repertoire of drugs available for evaluation in AIDS clinical trials.

Another area of priority for the NIH is the development of drugs with activity against opportunistic infections and this program is under development at NIAID. NIAID has a long history of involvement in the development of animal and _in vitro_ model systems for the identification of anti-infective and has logically undertaken this commitment. As an essential component of this effort, NIAID is developing the capacity to carry out the preclinical development of one anti-infective from this program every two years. This preclinical drug development capability was developed as a complement to the NCI preclinical drug development program and expands the number of drugs which can be developed at the NIH. There is coordination between the two programs, thereby facilitating the exchange of scientific expertise and availability of resources.

NCI conducts preclinical testing on promising new drugs that are identified in the AIDS Drug Screen. Three to four new anti-HIV drugs can undergo preclinical development per year. The decisions about which drugs are the most promising and should be taken forward to preclinical development are made by the AIDS Drug Development Decision Network Committee which includes NCI and NIAID scientists.

In conclusion, NCI and NIAID have well-delineated and separate responsibilities for AIDS Drug Development which are complementary and not overlapping. The technologies for the NCI and NIAID programs vary considerably; however, coordination does exist for the sharing of new ideas and technical know-how.

Mr. Roybal. According to the budget justifications, if the NCI's preclinical drug screening program identifies more than three or four high priority compounds in one year, it will be necessary to license their development to the private sector. What level of funding would be needed to accommodate each additional compound for in-house development at NCI?

Dr. Raub. The Developmental Therapeutics Program, National Cancer Institute (DTP/NCI) actually operates two distinct preclinical drug screening programs. The Preclinical Antitumor Screen will screen 10,000 compounds per year, and the Anti-HIV Drug Screen will screen a similar number of pure compounds per year. In addition, a major effort is underway to acquire and screen natural products in both of the individual screens. Therefore, the individual screens may each yield three to four high-priority anticancer or anti-AIDS drugs that will require further development within the existing resources of DTP.

The process of preclinical drug development that follows identification of a promising lead in the anticancer or anti-HIV screens involves confirmation of both in vitro and in vivo biologic data, drug synthesis or isolation, pharmacologic and toxicologic investigation, formulation and large scale production for clinical investigation. The budget for these essential developmental tasks has been relatively constant over the past few years for anticancer drugs (averaging approximately $8.0 million per year). In contrast, there has been an increase for the developmental capacity for anti-HIV drugs over the past two years from approximately $4.3 million to $8.2 million per year. Therefore, there are approximately $16 million dollars for NCI preclinical drug development. Prior estimates for the cost of developing a new anticancer or anti-AIDS drug have ranged from about $628 thousand to over $800 thousand per drug.

The actual cost for the preclinical development of a new drug can vary substantially depending on a number of factors (e.g., problems with synthesis, isolation, or formulation). Furthermore, the development of a natural product may incur the additional expenses associated with identification of the chemical structure, lead optimization studies, and the procurement process (i.e., isolation, fermentation, or semi-synthesis) may be more expensive than that associated with a synthetic compound. Therefore, if an estimate for the development of the average compound is in the range of $800 thousand, the current budget would permit the development of approximately 18 to 20 drugs. Currently, there are eight anti-HIV drugs in active development with six additional drugs undergoing refinement and lead optimization studies. Furthermore, there are ten anticancer drugs under active development with two additional drugs undergoing refinement and lead optimization studies. Thus, the level of funding that would be needed to accommodate each additional compound for inhouse development would average approximately $800 thousand to $1.0 million with the understanding that there is an inherent variation around this cost that might range from $600 thousand to $1.5 million. NCI staff have had extensive experience in the drug discovery and development process for anticancer drugs. Furthermore, investigators within the Division of Cancer Treatment, NCI (DCT/NCI) have played a critical role in the discovery and development of promising new drugs for the treatment of AIDS (e.g. AZT, ddI,). The staff within NCI have also served as consultants to the pharmaceutical industry in order to enhance the drug development process.

Mr. Roybal. What is the nature of the licensing agreements?

Dr. Raub. The issuance of a license provides a negotiated legal document which contains the specifications for achievement of goals by the pharmaceutical firm that will ultimately be directed towards the approval of the drug by the FDA. NCI has established an Office of Technology Development (OTD) that provides the expertise in dealing with NCI issues related to licensing of new drugs and in the establishment of Cooperative Research and Development Agreements (CRADAs) for sharing responsibility for product development. Furthermore, the NIH has an Office of Technology Transfer (OTT) that will assist the investigator and the NCI's Office of Technology Development in formulating the language of either the license or the CRADA. A meeting of the Technology Management Team is organized to include the investigator (inventor), representatives of both NIH/OTT and NCI/OTD, a representative of the Patent Branch/DHHS, and a representative of the National Technical Information Service (NTIS). During this meeting, several issues are examined including the strength of the patent application, the need for advertising the intended licensing opportunity in the Federal Register, and the actual procedure for licensing is reviewed. The DHHS uses the NTIS (U.S. Department of Commerce) as the licensing agent.

The licensing agreement stipulates expectations of accomplishment for the drug under development, a time-frame for completion of the assigned tasks, and an annual progress report is required. The annual report is filed with NTIS, and a copy is provided to the inventor (investigator) for comment. The comments and recommendations of the inventor are conveyed to the licensee. Recently, an effort has been made to include language in the license pertaining to the ultimate cost of the product for the patient. The Government realizes the necessity for the pharmaceutical industry to recover the investment in the developmental costs. However, the licensee is asked to acknowledge the concern of the Government that there be a reasonable relationship between the licensee's pricing of the licensed product and the health and safety needs of the public and that this relationship be supported by evidence. If, during the exclusive marketing term of the agreement, the licensee fails to provide the evidence upon reasonable request of the NCI, then NTIS has the right to require that the licensee grant sublicenses under the patent to responsible parties. Finally, if the defined workscope of the agreement is not fulfilled by the licensee or if the time-frame is not adequately met, then the NCI retains the right to rescind the license.

Mr. Roybal. What control over the progress of research does NCI have in these agreements?

Dr. Raub. Expertise in the areas of pharmacology, toxicology, drug synthesis and formulation, and assistance in dealing with the appropriate scientific counterparts at the FDA have been provided at no cost to industry to enhance the overall process of drug development. The interest in establishing a collaborative effort with the pharmaceutical industry for the development of effective drugs for the treatment of either cancer or AIDS results from the realization that a commitment to an exclusive in-house developmental approach would be prohibitively expensive. Cost-sharing with the private sector enhances the overall capacity of the NCI drug developmental program.

The involvement of the NCI in the actual drug discovery process provides an opportunity for the procurement of patent rights to promising or high-priority drugs obtained from the screens. The NCI has developed the capability to establish formal agreements with the private sector to achieve the goals of procuring active drugs for cancer and AIDS patients. In the event that the NCI actually holds the patent for a new drug and the decision has been made to further develop the drug through a consensus derived from members of an NCI Decision Network Committee, the decision regarding the responsibility for the developmental plans will be either to proceed intramurally or to seek private sector collaboration. This process of shared-responsibility for drug development can be in the form of a CRADA (i.e., cooperative research and developmental agreement) or could form the basis for issuing a license for the new drug with a particular pharmaceutical firm.

Mr. Roybal. What agreements regarding pricing are made when compounds are licensed out?

Dr. Raub. The NCI has developed the capacity to share the responsibility for new drug development with the pharmaceutical industry by forming CRADAs. The Government and the collaborator (e.g., pharmaceutical industry) agree to form a joint research and development team to conduct and monitor the research in accordance with the research plan. As a result of this agreement, the NIH may provide an option for a subsequent exclusive commercialization license with the collaborator. The license will specify the licensed fields of use, breadth of exclusivity, and royalties. The NIH has a concern that there be a reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public. Accordingly, exclusive commercialization licenses granted for NIH intellectual property rights may require that this relationship be supported by reasonable evidence. Therefore, these cooperative research agreements extend the capacity of the NCI to follow the exciting new leads that may evolve from the NCI drug screening programs.

ACTG TRIALS

Mr. Roybal. The Committee has expressed interest in the past in the demographics of patients enrolled in the ACTG trials. What progress has been made in enrolling women and minorities in the ACTG system?

Dr. Raub. Women are well represented in the NIAID clinical trials system. They participate in the studies to a higher degree than their rates of HIV infection: nine percent of U.S. AIDS cases are in women, compared to 11 percent of patient enrollment in the NIAID clinical trials system. Further, several of our studies specifically address the needs of HIV-infected women.

The NIAID has made progress in recruiting minorities into its clinical trials system; for example, the percentage of blacks in the trials rose from six percent in 1986 to 14 percent in 1989. There is still considerable room for improvement in this area, and we have strengthened our resolve to increase minority representation even further in our studies. We are using several means to increase the participation of minority populations in the clinical trials. A new RFA under development, entitled the Expansion of the AIDS Clinical Trial Group to Underrepresented Minorities, is expected to appear in the NIH guide early this year with the first awards anticipated for Fall 1990. Recognizing the importance of collecting data that includes minorities, we are working to increase minority participation in our studies through this RFA by several means, for example, by including provisions for bringing the necessary social services to potential minority participants.

Mr. Roybal. How does this recruitment compare to the demographic of patients in the CPCRA program?

Dr. Raub. The Community Programs for Clinical Research on the Acquired Immunodeficiency Syndrome (CPCRA) initiates a new level of clinical research on infection with HIV, by extending the opportunity for participation in HIV research activities to community clinicians and their patients. Because the program is just beginning to accrue patients, we cannot as yet determine the demographics of the participants.

The CPCRA is expected to expand the population base involved in HIV research as well as take advantage of the extraordinary expertise which has developed at the community level. Enabling the participation of community-based clinicians and organizations in clinical research extends participation in well-designed clinical studies to persons currently underrepresented in NIAID-supported HIV research -- specifically, minorities, sexual partners of HIV-infected persons, and intravenous drugs users.

Mr. Roybal. How many patients are part of the CPCRA system as compared to the ACTGs? What is the cost per patient within the ACTGs and the CPCRA?

Dr. Raub. The CPCRA is just beginning to get underway and is just starting to accrue patients. At this point, we cannot estimate the average cost for the data obtained for each patient in the program. The NIAID will be able to furnish you that information when it becomes available, probably within the next few months.

ONE PERCENT SET-ASIDE

Mr. Stokes. In addition to the reductions previously mentioned, the NIH appropriation is subject to a number of "taps", such as the 1 percent set-aside for evaluations, and a transfer of funds for the new agency for health care policy and research. How many such "taps" are there and by how much will they reduce the FY 1990 appropriation and FY 1991 request?

Dr. Raub. The NIH receives a number of "taps" from the PHS and the Office of the Secretary to support, for example, services, studies and reports, commissions established by Congress that are a benefit to the NIH and to the overall Department. Over the past several years, these "taps" have ranged from $3 to $4 million. We would expect FY 1991 to be in this same range.

HEALTH AND BEHAVIOR

Mr. Stokes. As you know, this committee is very interested in focusing federal efforts on improving public health and disease prevention, and exploring relationships between health and behavior. I understand that very soon NIH will be transmitting to the Senate a report on Health-Related Behavioral Research that was requested last year. Can you summarize how you will be responding to the directive in the FY 1990 Senate appropriation report, which urged NIH to increase the proportion of funding of health-related behavioral research?

Dr. Raub. Like the Committee, the NIH recognizes the contributions of behavioral factors to health and the need to assure adequate levels of support for research in this area. Towards this end, the NIH has taken steps to assess the current status of NIH-supported research on health and behavior and to consider future research directions and opportunities. The NIH submitted its report to the Senate Appropriations Committee at the end of February 1990. The report provides examples of future research directions such as behavioral epidemiology of stroke or sensory disorders; health-related behaviors affecting low-birth-weight infants or HIV-positive patients; basic biobehavioral mechanisms of obesity or arthritis; and behavioral interventions to prevent injuries or to improve the health of minorities. Moreover, this report puts into place a continuing process for an orderly development of a long-range plan.

The NIH views health-related behavioral research as an integral part of its research and training programs. Each NIH Institute will assess the potential contributions of health and behavior research to fulfilling its mandate, contingent upon the scientific quality of research applications received. In order to identify more fully this potential and to foster high quality applications, the NIH Working Group on Health and Behavior will coordinate an NIH-wide planning effort and deliver a set of recommendations to the Director, NIH, and the Institute Directors by September, 1990. These recommendations will include methods for improving the financial tracking of health and behavior research supported by NIH; identification of appropriate and promising research initiatives with each Institute; and plans for increasing the level of support for health and behavior research over a ten-year period. These recommendations, as discussed and approved by all NIH components, will then provide the report and long-term plan requested by the Senate.

ONE PERCENT TRANSFER AUTHORITY

Mr. Stokes. The President's budget includes a proposal that would give the NIH Director the ability to transfer up to one percent of NIH's appropriation in order to fund emerging or emergency research opportunities. Did NIH request such a discretionary fund for the Director?

Dr. Raub. The NIH did not request the one percent transfer authority. The NIH did request a Director's Discretionary Fund and $20 million is included in the 1990 President's budget for this purpose.

Mr. Stokes. Given the ability of the Institute Directors to direct funding by means of issuing "Requests for Proposals and Requests for Applications", why is it necessary to give the NIH Director this additional authority?

Dr. Raub. The NIH is a confederation of separate entities. As such it cannot always respond in the most efficient manner possible to new issues, emergencies, or research opportunities that do not clearly fall within the scope of one institute or another. In these circumstances the Director needs the resources to initiate activities across institute lines, without imposing on the independence of the institutes.

SILVER SPRING MONKEYS

Mr. Stokes. What is the status of the remaining "silver spring monkeys?" I know that one died recently. I received many letters expressing outrage that this monkey (Billy) was experimented on.

Dr. Raub. Seven monkeys remain at the Delta Regional Primate Research Center (Louisiana); one is a normal female rhesus monkey and six are cynomolgus males who underwent a surgical procedure (deafferentiation) many years ago to eliminate sensation from one forelimb. The knowledge gained from this experience has direct bearing on the search for new means to treat the consequences of spinal cord injuries and strokes. Four unoperated animals are being maintained at the San Diego Zoo. Three of the animals have been fully resocialized and one remains in social isolation because the animal harbors a virus which does not affect the monkey adversely, but is life threatening to human handlers.

On January 14, 1990, the NIH ordered euthanasia for one of the surgically disabled monkeys, Billy, because he was near death and attending veterinarians at the Delta Center had determined that his condition almost certainly would continue to deteriorate. Billy was one of eight monkeys that underwent forelimb differentation for experimental purposes about ten years ago. The operation involved cutting spinal nerves in such a way that the corresponding forelimb became permanently devoid of sensation.

The NIH took this action only after judges in two different Federal Courts approved the Government's request to lift previously issued restraining orders that had precluded NIH from taking this necessary step. The NIH was carrying out its responsibilities under the Public Health Service Act and the Animal Welfare Act.

The Silver Spring monkeys are subjects for research related to improving means to rehabilitate handicapped humans. No other laboratory animals ever have been maintained for so long a time with so large an area of the brain's sensory map affected. The information gathered during the euthanasia procedure is needed to determine whether and, if so, to what extent the brain has undergone a functional reorganization in the area that received signals from the affected forelimb before its sensory nerves were cut. Understanding how and by what mechanisms the central nervous system adapts to physical or chemical alterations--technically termed neural plasticity--is one of the most important objectives of modern neuroscience. Knowledge of this phenomonon bears directly on the search for new means to treat, and perhaps reverse, the consequences of spinal cord injuries and strokes in human beings and animals. The NIH believes it would be unethical not to study these monkeys in the way described above, for otherwise they will have borne their experimentally induced disabilities all these years in vain.

INFLATION FACTORS

Mr. Early. What will be the annual federal investment in medical research per person under your budget request?

Dr. Raub. The FY 1991 NIH request of $7,929,686,000 reflects an investment in medical research of approximately $31 per person.

Mr. Early. Doctor, what kind of inflation factor or allowance was used in developing this budget request?

Dr. Raub. The OMB GNP deflator of 4.2 percent was used in developing the budget request.

Mr. Early. Wouldn't the biomedical research and development price index (BRDPI) be a more accurate indicator?

Dr. Raub. The BRDPI was developed for the NIH by the Bureau of Economic Analysis, Department of Commerce. The relative weights used to construct the BRDPI reflect the actual pattern of expenditure on inputs for biomedical research supported by the NIH. For this reason, it is more indicative of the inflationary costs likely to be experienced by the research community, compared to other inflation indicators.

Mr. Early. Isn't it true that the BRDPI is generally higher than the GNP deflator (and CPI)--usually by about 2 points anyway?

Dr. Raub. The BRDPI is generally higher than the GNP. The amount of difference varies year to year. The following table compares annual percent changes in the GNP Implicit Price Deflator to annual percent changes in the BRDPI from 1983 to 1989.

Annual Percent Changes

	GNP Implicit Price Deflator	BRDPI
1983........	4.2	6.0
1984........	3.8	5.8
1985........	3.1	5.1
1986........	2.7	4.2
1987........	3.0	5.4
1988........	3.0	5.0
1989........	4.2	5.2

Mr. Early. The budget request contains a 4.7 percent increase (current dollars) for NIH for FY 1991. What does this translate to in constant dollars?

Dr. Raub. Using the GNP deflator, the request constitutes an increase of 0.4 percent in constant dollars. Using the Biomedical Research & Development Price Index (BRDPI), the change in constant dollars from FY 1990 is a reduction of 1.1 percent.

Mr. Early. What would these increases be exclusive of AIDS?

Dr. Raub. Exclusive of AIDS, using the GNP deflator, the request reflects an increase of 0.1 percent. Exclusive of AIDS, using the BRDPI, the request reflects a 1.4 percent reduction from FY 1990.

Mr. Early. Can you give us the constant dollar increase for FY 1990 and FY 1989?

Dr. Raub. Including AIDS, using the GNP deflator, FY 1989 reflects a 2.8 percent increase over FY 1988; using the BRDPI, FY 1989 reflects a 1.9 percent increase over FY 1988.

Excluding AIDS, using the GNP deflator, FY 1989 reflects a 1.4 percent increase over FY 1988; using the BRDPI, FY 1989 reflects a 0.4 percent increase over FY 1988.

Including AIDS, using the GNP deflator, FY 1990 reflects a 2.0 percent increase over FY 1989; using the BRDPI, FY 1990 reflects a 0.3 percent increase over 1989.

Excluding AIDS, using the GNP deflator, FY 1990 reflects a 0.4 percent increase over FY 1989; using the BRDPI, FY 1990 reflects a 1.2 percent reduction from FY 1989.

Mr. Early. The justification states that noncompeting grants will receive an average increase of 5.8 percent and competing grants will receive an average increase of 2 percent. If we translated these figures into constant dollars, what would they be?

Dr. Raub. Using the GNP deflator, average costs for noncompeting awards would increase 1.5 percent; using the BRDPI average costs would remain about constant. Using the GNP deflator, average costs for competing awards would decrease 2.1 percent; using the BRDPI, average costs would decrease 3.6 percent.

INCREASES IN AVERAGE COST

Mr. Early. Doctor, how did you determine these average cost increases?

Dr. Raub. These average cost increases were determined in the context of the overall budget request after consideration of all of the NIH funding priorities. The resulting average cost increase were therefore determined in conjunction with the number of competing research project grants to be funded and the level of downward negotiations.

COMPETING RESEARCH PROJECT GRANTS

Mr. Early. Why will competing grants receive an increase well below even the GNP deflator?

Dr. Raub. Many difficult choices were made in the development of the FY 1991 budget. NIH proposed these average cost increases so that it could maintain overall program balance between the various funding mechanisms, fund a sufficient number of competing research project awards, and provide increases for a few selected priority areas.

FY 1991 BUDGET FORMULATION PROCESS

Mr. Early. Doctor, will you describe the process used to determine the FY 1991 budget request for NIH?

Dr. Raub. The budget process began with the identification of FY 1991 planning assumptions, areas of scientific opportunity, and policy, legislative, and budget issues. This was followed by Institute planning sessions with Dr. Wyngaarden. Soon after this, the Institutes submitted their professional judgment budgets to NIH. From these budget submissions, the NIH preliminary request was formulated and forwarded to PHS. This submission to the PHS represented our budget priorities and strategies within the overall guidelines established by the PHS. NIH was next given an initial PHS allowance followed by NIH appeals and a final PHS allowance, which became the NIH budget submission to the Office of the Secretary, DHHS. The same process of budget submission, initial allowances, budget appeals, and final allowances was repeated for the Department and OMB. The President's final decision became the FY 1991 President's budget, which was submitted to the Congress.

Mr. Early. What was the aggregate amount of the budget requests submitted by the Institutes, NLM, etc. to you office? What would the amount be exclusive of AIDS?

Dr. Raub. The total amount requested by the Institutes for 1991 was $11,679,578,000, of which $10,300,734,000 was related to non-AIDS activities and $1,378,844,000 was for AIDS.

Mr. Early. What was the amount of NIH's budget request to the Public Health Service? What would this be exclusive of AIDS?

Dr. Raub. The NIH request to the Public Health Service was $11,058,473,000 in total. The amount for non-AIDS was $9,780,064,000 and $1,278,409,000 was requested for AIDS.

Mr. Early. What was the PHS submission to the Department? What would this be exclusive of AIDS?

Dr. Raub. The PHS request to the Department of Health and Human Services was $8,435,648,000 of which $7,437,868,000 was for non-AIDS and $997,780,000 was for AIDS.

Mr. Early. The Department's request to OMB? What was this exclusive of AIDS?

Dr. Raub. The Department's request to OMB was $7,992,094,000 of which $7,155,905,000 was for non-AIDS and $836,189 000 was for AIDS.

CHRONOLOGY OF THE FY 1991 BUDGET

Mr. Early. Please provide for the record a table displaying, by Institute, the budget request at each of these stages. Also provide for the record a mechanism table for each Institute displaying the requests at each of these stages.

Dr. Raub. The following tables display by Institute the amounts the ICDs requested of NIH, the DHHS request to OMB and the President's budget. The NIH estimate to the PHS and the PHS estimate to DHHS were submitted in total and the information is not available by Institute.

Mechanism tables by ICD are submitted for the ICD estimate to NIH, the OMB submission and the President's Budget. Since the other submissions were in total, mechanism tables are not available by Institute and are submitted in NIH summary.

BUDGET DEVELOPMENT

Mr. Early. Doctor, did NIH receive any specific instructions from PHS, HHS, or OMB as to the content of the request that should or could be sent forward to PHS/HHS/OMB?

Dr. Raub. Each year, the PHS provides NIH with technical instructions for the development of the preliminary budget submission. The PHS FY 1991 preliminary budget instructions stated that FY 1991 should be based on the estimates and policies reflected in the FY 1990 President's budget.

After review by the PHS, NIH received guidance on the funding levels to be requested in its portion of the PHS budget submission to the Secretary, DHHS. These request levels represented the views of the Assistant Secretary for Health after considering all the priorities of the various PHS agencies. The same process was repeated for the Department and OMB.

Mr. Early. Were you given a limit, either in terms of numbers or dollars, on what you could propose for total research grants? New and competing grants? Research centers?

Dr. Raub. We were not given any limits on any of the mechanisms that comprise the NIH budget.

Mr. Early. Doctor, were you permitted to take an appeal to PHS or the Department on this budget request?

Dr. Raub. Yes, we were permitted to appeal the allowances.

Mr. Early, Did the Department take an appeal to OMB?

Dr. Raub. Yes, the Department did take our appeal.

RESEARCH PROJECT GRANTS

Mr. Early. Doctor, the FY 1991 budget request funds 5,095 new and competing grants, 4,856 exclusive of AIDS. Aside from FY 1990,

DHHS - National Institutes of Health

Chronology of the 1991 President's Budget

(Dollars in thousands)

	1990 COMPARABLE			1991 ICD ESTIMATE TO NIH			1991 NIH ESTIMATE TO PHS 1/			1991 PHS ESTIMATE TO DHHS 1/		
	Non-AIDS	AIDS	TOTAL	Non-AIDS	AIDS	TOTAL	Non-AIDS	AIDS	TOTAL	Non-AIDS	AIDS	TOTAL
NCI..........	$1,483,990	$150,304	$1,634,294	$2,192,488	$218,569	$2,411,057						
NHLBI........	1,030,279	42,056	1,072,335	1,414,640	71,761	1,486,401						
NIDR.........	131,082	4,662	135,744	235,559	12,899	248,458						
NIDDK........	576,146	5,320	581,466	771,300	37,091	808,391						
NINDS........	474,238	16,158	490,396	631,215	44,163	675,378						
NIAID........	439,002	393,958	832,960	607,858	592,424	1,200,282						
NIGMS........	697,416	14,614	712,030	889,064	20,736	909,800						
NICHD........	416,157	26,749	442,906	605,762	106,775	712,537						
NEI..........	230,996	5,533	236,529	330,198	8,414	338,612						
NIEHS........	224,942	4,291	229,233	287,237	4,815	292,052						
NIA..........	238,593	859	239,452	467,112	13,337	480,449						
NIAMS........	167,689	1,238	168,927	269,180	7,505	276,685						
NIDCD........	117,582	---	117,582	142,641	1,220	143,861						
DRR..........	291,009	46,096	337,105	514,567	121,362	635,929						
NCNR.........	32,526	987	33,513	42,905	5,285	48,190						
NCHGR........	59,538	---	59,538	175,935	---	175,935						
FIC..........	10,758	4,898	15,656	16,837	9,501	26,338						
Subtot.,ICDs.	6,621,943	717,723	7,339,666	9,594,498	1,275,857	10,870,355						
NLM..........	85,235	493	85,728	164,626	3,000	167,626						
OD...........	79,365	10,551	89,916	154,010	14,487	168,497						
B & F........	46,277	14,765	61,042	387,600	85,500	473,100						
TOTAL, NIH..	6,832,820	743,532	7,576,352	10,300,734	1,378,844	11,679,578	$9,780,064	$1,278,409	$11,058,473	$7,437,868	$997,780	$8,435,648

1/ Estimate submitted in total, information not available by BID.
2/ Excludes $21,780 and 100 noncompeting grants from the 1990 Directors Discretionary fund.

Chronology of the 1991 President's Budget - Cont'd

(Dollars in thousands)

	1991 DHHS ESTIMATE TO OMB [2/]			1991 PRESIDENT'S BUDGET		
	Non-AIDS	AIDS	TOTAL	Non-AIDS	AIDS	TOTAL
NCI..........	$1,553,143	$167,059	$1,720,202	$1,533,252	$160,807	$1,694,059
NHLBI........	1,082,140	46,764	1,128,904	1,068,039	44,463	1,112,502
NIDR.........	136,162	4,740	140,902	135,518	5,002	140,520
NIDDK........	602,780	6,089	608,869	599,558	5,791	605,349
NINDS........	499,072	18,110	517,182	494,985	17,227	512,212
NIAID........	464,988	445,417	910,405	463,468	423,407	886,875
NIGMS........	733,289	16,414	749,703	730,007	15,487	745,494
NICHD........	434,080	31,620	465,700	432,463	29,010	461,473
NEI..........	244,637	6,284	250,921	241,505	5,887	247,392
NIEHS........	232,794	4,823	237,617	231,212	4,580	235,792
NIA..........	239,520	969	240,489	248,009	929	248,938
NIAMS........	174,792	1,553	176,345	174,597	1,483	176,080
NIDCD........	104,430	600	105,030	122,269	578	122,847
DRR..........	253,000	49,350	302,350	270,772	48,379	319,151
NCNR.........	31,379	1,209	32,588	33,979	1,148	35,127
NCHGR........	133,000	---	133,000	108,029	---	108,029
FIC..........	10,912	5,409	16,321	11,148	5,207	16,355
Subtot.,ICDs.	6,930,118	806,410	7,736,528	6,898,810	769,385	7,668,195
NLM..........	81,430	553	81,983	89,384	532	89,916
OD...........	72,257	12,726	84,983	69,228	13,747	82,975
B & F........	72,100	16,500	88,600	72,100	16,500	88,600
TOTAL, NIH..	7,155,905	836,189	7,992,094	7,129,522	800,164	7,929,686

1/ Estimate submitted in total, information not available by BID.

2/ Excludes $21,780 and 100 noncompeting grants from the 1990 Directors Discretionary fund.

DHHS-National Institutes of Health
CHRONOLOGY OF THE 1991 PRESIDENT'S BUDGET BY MECHANISM

(Dollars in thousands)

	1991 ICD Request to NIH					
	Non-AIDS		AIDS **		Total	
Research Grants	No.	Amount	No.	Amount	No.	Amount
Research Proj.:						
Noncompeting	14983	$3,417,335	778	$341,126	15761	$3,758,461
Admin. suppl.	(555)	30,204	(5)	112	(560)	30,316
Competing	8817	1,950,945	625	201,542	9,442	2,152,487
Subtotal, RPG	23800	5,398,484	1403	542,780	25203	5,941,264
Research Centers:						
Spec./comp.	543	686,470	26	29,969	569	716,439
GCRC	83	128,222	--	34,053	83	162,275
Biotech	66	51,764	--	1,846	66	53,610
LASPR	18	22,000	11	22,057	29	44,057
RCMI	55	46,516	--	7,451	55	53,967
Subtotal, Ctrs	765	934,972	37	95,376	802	1,030,348
Other Research:						
Careers	2065	150,333	9	634	2074	150,967
Clin. ed	52	5,570	--	---	52	5,570
Coop. Clin.	458	126,420	21	10,579	479	136,999
BRS	837	139,447	100	12,298	937	151,745
MBRS	98	55,388	--	209	98	55,597
Other	1731	133,906	43	10,595	1774	144,501
Subtotal	5241	611,064	173	34,315	5414	645,379
Total, Res. Grt	29806	6,944,520	1613	672,471	31419	7,616,991
Training						
Individual	2656	77,600	96	2,741	2752	80,341
Institutional	11186	301,807	323	8,000	11509	309,807
Total, Trng.	13842	379,407	419	10,741	14261	390,148
R&D Contracts	1879	684,539	463	329,184		1,013,723
Intramural		904,132		177,613		1,081,745
RMS		353,553		38,198		391,751
Control		156,597		---		156,597
Construction		171,750		47,650		219,400
Subtotal, IRDs		9,594,498		1,275,857		10,870,355
NLM		164,626		3,000		167,626
OD		154,010		14,487		168,497
B&F		387,600		85,500		473,100
Total, NIH		10,300,734		1,378,844		11,679,578

Note--Excludes $200 in permanent budget authority expected to be derived from Cooperative Research and Development Agreements.

CHRONOLOGY OF THE 1991 PRESIDENT'S BUDGET BY MECHANISM - Cont'd

(Dollars in thousands)

1991 NIH Request to PHS

	Non-AIDS		AIDS		Total	
Research Grants	No.	Amount	No.	Amount	No.	Amount
Research Proj.:						
Noncompeting	15083	$3,401,799	748	$321,834	15831	$3,723,633
Admin. suppl.	(450)	27,000	(5)	112	(455)	27,112
Competing	8250	1,838,190	613	181,898	8,863	2,020,088
Subtotal, RPG	23333	5,266,989	1361	503,844	24694	5,770,833
Research Centers:						
Spec./comp.	509	624,007	24	28,224	533	652,231
GCRC	83	130,000	--	28,953	83	158,953
Biotech	66	47,000	--	382	66	47,382
LASPR	46	45,000	11	22,057	57	67,057
RCMI	18	22,000	--	7,451		
Subtotal, Ctrs	722	868,007	35	87,067	739	925,623
Other Research:						
Careers	2000	145,600	9	634	2009	146,234
Clin. ed	28	3,000	--	---	28	3,000
Coop. Clin.	353	93,694	21	10,579	374	104,273
BRS	837	140,000	--	790	837	140,790
MBRS	98	48,493	--	209	98	48,702
Other	1546	108,261	43	10,595	1589	118,856
Subtotal	4862	539,048	73	22,807	4935	561,855
Total, Res. Grt	28917	6,674,044	1469	613,718	30368	7,258,311
Training						
Individual	2136	59,879	96	2,741	2232	62,620
Institutional	10564	278,124	323	8,000	10887	286,124
Total, Trng.	12700	338,003	419	10,741	13119	348,744
R&D Contracts	1655	570,000	224	298,267	1879	868,267
Intramural		940,000		175,192		1,115,192
RMS		335,000		36,503		371,503
Control		100,000		---		100,000
Construction		175,000		41,250		216,250
Subtotal, IRDs		9,132,047		1,175,671		10,278,267
NLM		105,000		3,000		108,000
OD		150,017		14,238		164,255
B&F		393,000		85,500		478,500
Total, NIH		9,780,064		1,278,409		11,029,022

Note--Excludes $200 in permanent budget authority expected to be derived from Cooperative Research and Development Agreements.

CHRONOLOGY OF THE 1991 PRESIDENT'S BUDGET BY MECHANISM - Cont'd

(Dollars in thousands)

	1991 PHS Request to DHHS					
	Non-AIDS		AIDS		Total	
Research Grants	No.	Amount	No.	Amount	No.	Amount
Research Proj.:						
Noncompeting	15083	$3,205,575	626	$288,022	15709	$3,493,597
Admin. suppl.	(460)	19,551	(2)	59	(462)	19,610
Competing	4843	1,064,039	417	123,712	5,260	1,187,751
Subtotal, RPG	19926	4,289,165	1043	411,793	20969	4,700,958
Research Centers:						
Spec./comp.	392	430,252	15	23,185	407	453,437
GCRC	78	98,997	--	23,953	78	122,950
Biotech	62	37,366	--	382	62	37,748
LASPR	40	34,540	11	17,857	51	52,397
RCMI	18	16,462	--	5,758	18	22,220
Subtotal, Ctrs	590	617,617	26	71,135	616	688,752
Other Research:						
Careers	1631	116,953	7	489	1638	117,442
Clin. ed	21	2,151	--	---	21	2,151
Coop. Clin.	229	69,821	11	5,484	240	75,305
BRS	137	34,876	--	790	137	35,666
MBRS	98	42,076	--	196	98	42,272
Other	1100	67,829	29	9,079	1129	76,908
Subtotal	3216	333,706	47	16,038	3263	349,744
Total, Res. Grt	23732	5,240,488	1116	498,966	24848	5,739,454
Training						
Individual	1926	51,943	67	2,017	1993	53,960
Institutional	9574	241,043	321	8,541	9895	249,584
Total, Trng.	11500	292,986	388	10,558	11888	303,544
R&D Contracts	1200	402,976	358	241,650	1558	644,626
Intramural		804,293		151,428		955,721
RMS		304,085		28,374		332,459
Control		78,313		---		78,313
Construction		---		---		---
Subtotal, IRDs		7,123,141		930,976		8,054,117
NLM		84,446		3,333		87,779
OD		74,981		14,271		89,252
B&F		155,300		49,200		204,500
Total, NIH		7,437,868		997,780		8,435,648

Note--Excludes $200 in permanent budget authority expected to be derived from Cooperative Research and Development Agreements.

CHRONOLOGY OF THE 1991 PRESIDENT'S BUDGET BY MECHANISM - Cont'd

(Dollars in thousands)

1991 DHHS Request to OMB

	Non-AIDS		AIDS		Total	
Research Grants	No.	Amount	No.	Amount	No.	Amount
Research Proj.:						
Noncompeting	14983	$3,176,535	626	$282,464	15609	$3,458,999
Admin. suppl.	(475)	19,939	(2)	59	(477)	19,998
Competing	4706	1,047,854	188	55,302	4,894	1,103,156
Subtotal, RPG	19689	4,244,328	814	337,825	20503	4,582,153
Research Centers:						
Spec./comp.	397	400,647	12	16,825	409	417,472
GCRC	78	92,955	--	23,953	78	116,908
Biotech	62	35,251	--	382	62	35,633
LASPR	40	32,585	11	17,857	51	50,442
RCMI	18	18,462	--	2,695	18	21,157
Subtotal, Ctrs	595	579,900	23	61,712	618	641,612
Other Research:						
Careers	1564	108,546	7	489	1571	109,035
Clin. ed	20	2,082	4	4,309	24	6,391
Coop. Clin.	229	67,590	--	790	229	68,380
BRS	137	34,068	--	196	137	34,264
MBRS	98	42,076	--	--	98	42,076
Other	1101	65,954	29	7,480	1130	73,434
Subtotal	3149	320,316	40	13,264	3189	333,580
Total, Res. Grt	23433	5,144,544	877	412,801	24,310	5,557,345
Training						
Individual	1901	49,792	48	1,385	1949	51,177
Institutional	9415	228,014	255	6,108	9670	234,122
Total, Trng.	11316	277,806	303	7,493	11619	285,299
R&D Contracts	1186	373,420	330	219,881	1516	593,301
Intramural		768,803		138,773		907,576
RMS		289,931		27,462		317,393
Control		74,614		---		74,614
Construction		1,000		---		1,000
Subtotal, IRDs		6,930,118		806,410		7,736,528
NLM		81,430		553		81,983
OD		72,257		12,726		84,983
B&F		72,100		16,500		88,600
Total, NIH		7,155,905		836,189		7,992,094

Note--Excludes $200 in permanent budget authority expected to be derived from Cooperative Research and Development Agreements.

Excludes $21,770 and 100 noncompeting grants from the 1990 Director's Discretionary Fund.

CHRONOLOGY OF THE 1991 PRESIDENT'S BUDGET BY MECHANISM - Cont'd

(Dollars in thousands)

	1991 President's Budget					
	Non-AIDS		AIDS		Total	
Research Grants	No.	Amount	No.	Amount	No.	Amount
Research Proj.:						
Noncompeting	14731	$3,075,714	613	$269,451	15344	$3,345,165
Admin. suppl.	(432)	21,037	(2)	59	(434)	21,096
Competing	4856	1,011,946	239	46,568	5095	1,058,514
Subtotal, RPG	19587	4,108,697	852	316,078	20439	4,424,775
Research Centers:						
Spec./comp.	412	430,158	12	15,589	424	445,747
GCRC	78	92,651	--	23,431	78	116,082
Biotech	59	31,706	--	381	59	32,087
LASPR	42	33,175	11	17,868	53	51,043
RCMI	20	20,595	--	4,072	20	24,667
Subtotal, Ctrs	611	608,285	23	61,341	634	669,626
Other Research:						
Careers	1528	104,137	16	1,088	1544	105,225
Clin. ed	29	2,942	--	---	29	2,942
Coop. Clin.	245	73,527	3	3,837	248	77,364
BRS	810	52,174	--	792	810	52,966
MBRS	98	42,785	--	260	98	43,045
Other	1161	68,317	31	7,850	1192	76,167
Subtotal	3871	343,882	50	13,827	3921	357,709
Total, Res. Grt	24069	5,060,864	925	391,246	24994	5,452,110
Training						
Individual	1916	49,659	72	1,965	1988	51,624
Institutional	9799	234,461	233	5,538	10032	239,999
Total, Trng.	11715	284,120	305	7,503	12020	291,623
R&D Contracts	1064	384,915	292	207,994	1356	592,909
Intramural		780,021		134,892		914,913
RMS		311,952		27,750		339,702
Control		75,459		---		75,459
Construction		1,479		---		---
Subtotal, IRDs		6,898,810		769,385		7,668,195
NLM		89,384		532		89,916
OD		69,228		13,747		82,975
B&F		72,100		16,500		88,600
Total, NIH		7,129,522		800,164		7,929,686

DHHS - National Institutes of Health
FY 1991 ICDs SUBMISSION TO NIH
(Dollars in thousands)
INCLUDES AIDS

Research Grants	NCI		NHLBI		NIDR		NIDDK		NINDS		NIAID		NIGMS		NICHD		NEI		NIEHS	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:																				
Noncompeting	2357	$661,601	2142	$597,664	282	$54,760	1662	$367,134	1472	$296,092	1669	$465,414	2327	$470,852	1133	$271,121	866	$150,524	289	$58,002
Admin. supp.	(140)	7,231	(60)	4,051	(4)	252	(40)	1,341	(90)	3,300	(26)	1,170	(17)	700	(70)	3,000	(30)	1,259	(20)	868
Competing...	*****	364,159	1,185	330,918	248	51,690	976	210,500	795	160,830	1,069	275,564	1,277	236,454	646	145,362	429	77,289	153	31,502
Subtot.,RPG.	3875	1,032,991	3327	932,633	530	106,702	2638	578,975	2267	460,222	2738	742,148	3604	708,006	1779	419,483	1295	229,072	442	90,372
Research Ctrs:																				
Spec/comp...	65	144,794	80	124,902	30	27,750	55	60,500	48	45,000	49	41,898	15	10,733	65	57,555	35	13,125	19	22,108
GCRC........																				
Biotech.....																				
LASPR.......																				
Gorgas......																				
RCMI........																				
Subtotal..	65	144,794	80	124,902	30	27,750	55	60,500	48	45,000	49	41,898	15	10,733	65	57,555	35	13,125	19	22,108
Other Res.:																				
Careers	183	13,000	551	38,714	178	13,214	200	14,400	255	17,715	122	8,797	34	2,065	140	10,343	35	2,450	30	2,090
Clin. ed....	52	5,570																		
Coop. cl....	295	94,259	14	2,868					4	4,680					32	10,083	134	25,109		
BRS.........																				
MBRS........		3,300		5,033		1,550		2,000		250		814	98	39,072		1,000		450		700
Other.......	372	20,517	149	16,347	116	3,480	60	4,000	103	4,500	90	4,772	82	4,193	75	3,800	94	3,812	22	1,241
Subtotal..	902	136,646	714	62,962	294	18,244	260	20,400	362	27,145	212	14,383	214	45,330	247	25,226	263	31,821	52	4,031
Total,RGs...	4842	1,314,431	4121	1,120,497	854	152,696	2953	659,875	2677	532,367	2999	798,429	3833	764,069	2091	502,264	1593	274,018	513	116,511
Training																				
Indiv.......	225	6,261	262	8,096	52	1,810	200	5,200	235	6,414	194	7,909	788	24,027	150	4,578	114	3,609	50	1,324
Instit......	1375	38,940	1538	48,953	348	10,231	800	22,600	470	12,307	506	13,357	3826	91,119	704	19,542	175	4,921	450	10,104
Total, Trng.	1600	45,201	1800	57,049	400	12,041	1000	27,800	705	18,721	700	21,266	4614	115,146	854	24,120	289	8,530	500	11,428
R&D Contracts.	881	353,435	299	146,396	124	31,332	45	20,000	77	21,500	260	172,845	7	6,691	240	95,972	65	8,500	226	75,360
Intramural ...		387,084		101,990		40,307		77,716		79,784		150,581		1,163		65,458		26,786		80,177
RM&S		92,909		52,469		12,082		23,000		23,006		57,161		22,731		24,723		10,778		8,576
Control.......		156,597																		
Construction..		61,400		8,000														10,000		
Total, IRDs...		2,411,057		1,486,401		248,458		808,391		675,378		1,200,282		909,800		712,537		338,612		292,052

DHHS - National Institutes of Health
FY 1991 ICDs SUBMISSION TO NIH

Research Grants	NIA No.	NIA Amount	NIAMS No.	NIAMS Amount	NIDCD No.	NIDCD Amount	DRR No.	DRR Amount	NCNR No.	NCNR Amount	NCHGR No.	NCHGR Amount	FIC No.	FIC Amount	TOTAL No.	TOTAL Amount
Research Proj.:																
Noncompeting	475	$118,744	494	$96,266	267	$58,231			94	$18,625	232	$73,431			15761	$3,758,461
Admin. supp.	(39)	6,152	(15)	483	(6)	300			(3)	209					(560)	30,316
Competing...	402	105,169	444	87,059	155	37,010			65	13,061	80	25,920			9442	2,152,487
Subtot.,RPG.	877	230,065	938	183,808	422	95,541			159	31,895	312	99,351			25203	5,941,264
Research Ctrs:																
Spec/comp...	36	83,676	34	34,761	17	20,500	83	128,222	11	4,137	10	25,000			652	844,661
GCRC........							66	$85,817							66	85,817
Biotech.....							18	23,846							18	23,846
LASPR.......							66	68,573							66	68,573
Gorgas......																
RCMI........								7,451								7,451
Subtotal..	36	83,676	34	34,761	17	20,500	233	313,909	11	4,137	10	25,000			802	1,030,348
Other Res.:																
Careers	113	11,687	83	6,313	60	4,188	16	1,006	24	1,633	50	3,352			2074	150,967
Clin. ed....															52	5,570
Coop. cl....															479	136,999
BRS.........							937	151,745							937	151,745
MBRS........		728		600		100									98	55,597
Other.......	58	2,914	24	3,005	17	826	266	53,620	6	520	12	1,332	228	15,622	1774	144,501
Subtotal..	171	15,329	107	9,918	77	5,114	1219	206,371	30	2,153	62	4,684	228	15,622	5414	645,379
Total,RGs...	1084	329,070	1079	228,487	516	121,155	1452	520,280	200	38,185	384	129,035	228	15,622	31419	7,616,991
Training																
Indiv.......	56	1,702	70	2,231	50	1,321	6	192	200	3,085	100	2,582			2752	80,341
Instit......	500	14,458	243	8,137	125	3,425	96	3,554	96	2,741	257	5,418			11509	309,807
Total, Trng.	556	16,160	313	10,368	175	4,746	102	3,746	296	5,826	357	8,000			14261	390,148
R&D Contracts.	72	44,130	17	10,978	10	3,270	9	7,752	4	562	6	15,000			2342	1,013,723
Intramural ...		44,903		17,706		7,690				400						1,081,745
RM&S		16,186		9,146		7,000		14,151		3,217		3,900		10,716		391,751
Control.......																156,597
Construction..		30,000						90,000				20,000				219,400
Total IRDs...		480,449		276,685		143,861		635,929		48,190		175,935		26,338		10,870,355

National Library of Medicine...	167,626
Office of the Director.........	168,497
Buildings and Facilities.......	473,100
TOTAL, NIH...............	11,679,578

DHHS - National Institutes of Health
FY 1991 SUBMISSION TO OMB
(Dollars in thousands)
INCLUDES AIDS

	NCI		NHLBI		NIDR		NIDDK		NINDS		NIAID		NIGMS		NICHD		NEI		NIEHS	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:																				
Noncompeting	2357	$609,768	2128	$549,790	284	$51,650	1594	$325,924	1445	$265,282	1645	$453,838	2327	$438,225	1092	$216,398	866	$143,718	289	$57,640
Admin. supp.	(140)	7,000	(60)	1,888	(4)	252	(40)	1,341	(66)	2,438	(23)	1,117	(17)	644	(40)	1,322	(30)	1,219	(10)	627
Competing...	728	190,227	652	179,588	95	16,535	495	106,461	445	94,174	520	118,413	786	150,825	374	73,559	229	39,456	78	15,827
Subtot.,RPG.	3085	806,995	2780	731,266	379	68,437	2089	433,726	1890	361,894	2165	573,368	3113	589,694	1466	291,279	1095	184,393	367	74,094
Research Ctrs:																				
Spec/comp...	60	101,501	64	87,897	18	14,285	40	33,487	29	22,495	28	19,937	15	9,352	46	33,206	27	6,908	16	16,033
GCRC........																				
Biotech.....																				
LASPR.......																				
Gorgas......																				
RCMI........																				
Subtotal..	60	101,501	64	87,897	18	14,285	40	33,487	29	22,495	28	19,937	15	9,352	46	33,206	27	6,908	16	16,033
Other Res.:																				
Careers	124	8,439	410	27,756	129	9,290	178	12,381	216	14,527	97	6,747	26	1,453	115	8,043	24	1,742	23	1,552
Clin. ed....	20	2,082																		
Coop. cl....	189	59,724	14	2,776					1	948							29	8,451		
BRS.........																				
MBRS........		3,096		2,659		177		1,607		217		742	98	31,566		576		323		438
Other.......	156	8,469	112	7,161	58	1,585	60	3,512	66	2,433	65	3,506	75	3,940	63	1,773	64	2,322	13	766
Subtotal..	489	81,810	536	40,352	187	11,052	238	17,500	283	18,125	162	10,995	199	36,959	178	10,392	117	12,838	36	2,756
Total,RGs...	3634	990,306	3380	859,515	584	93,774	2367	484,713	2202	402,514	2355	604,300	3327	636,005	1690	334,877	1239	204,139	419	92,883
Training																				
Indiv.......	180	4,641	206	5,939	28	881	160	4,026	175	4,624	146	4,029	496	13,634	99	2,733	99	2,870	40	966
Instit......	1276	31,551	1364	37,925	184	4,905	704	19,220	360	9,123	375	10,083	3409	71,436	534	13,423	155	3,958	385	8,416
Total, Trng.	1456	36,192	1570	43,864	212	5,786	864	23,246	535	13,747	521	14,112	3905	85,070	633	16,156	254	6,828	425	9,382
R&D Contracts.	535	208,903	242	90,174	25	4,578	34	11,616	62	11,522	179	125,872	7	5,920	124	37,308	51	6,935	187	60,598
Intramural ...		335,307		89,876		27,987		70,217		68,334		124,025		1,080		56,162		24,269		67,438
RM&S		73,880		45,475		8,777		19,077		21,065		42,096		21,628		21,197		8,750		7,316
Control.......		74,614																		
Construction..		1,000																		
Total, IRDs...		1,720,202		1,128,904		140,902		608,869		517,182		910,405		749,703		465,700		250,921		237,617

DHHS - National Institutes of Health
FY 1991 SUBMISSION TO OMB

	NIA		NIAMS		NIDCD		DRR		NCNR		NCHGR		FIC		TOTAL	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:																
Noncompeting	467	$107,194	496	$87,276	294	$63,429			93	$15,436	232	$73,431			15609	$3,458,999
Admin. supp.	(16)	852	(13)	381	(15)	715			(3)	202					(477)	19,998
Competing...	146	38,601	155	31,644	90	20,032			41	7,879	60	19,935			4894	1,103,156
Subtot.,RPG.	613	146,647	651	119,301	384	84,176			134	23,517	292	93,366			20503	4,582,153
Research Ctrs:																
Spec/comp...	18	21,899	26	22,124	9	7,461			5	1,087	8	19,800			409	417,472
GCRC........							78	$116,908							78	116,908
Biotech.....							62	35,633							62	35,633
LASPR.......							51	50,442							51	50,442
Gorgas......																
RCMI........							18	21,157								21,157
Subtotal..	18	21,899	26	22,124	9	7,461	209	224,140	5	1,087	8	19,800			600	641,612
Other Res.:																
Careers	88	7,232	53	3,909	32	2,162	9	561	12	904	35	2,337			1571	109,035
Clin. ed....															20	2,082
Coop. cl....															233	71,899
BRS.........							137	34,858							137	34,858
MBRS........		500		371											98	42,272
Other.......	30	1,667	21	2,040	4	246	128	22,718	4	297	4	544	207	10,455	1130	73,434
Subtotal..	118	9,399	74	6,320	36	2,408	274	58,137	16	1,201	39	2,881	207	10,455	3189	333,580
Total,RGs...	749	177,945	751	147,745	429	94,045	483	282,277	155	25,805	339	116,047	207	10,455	24310	5,557,345
Training																
Indiv.......	31	913	35	1,085	28	716	6	186	150	2,127	70	1,807			1949	51,177
Instit......	316	7,776	203	6,256	80	2,122	69	2,392	67	1,558	189	3,978			9670	234,122
Total, Trng.	347	8,689	238	7,341	108	2,838	75	2,578	217	3,685	259	5,785			11619	285,299
R&D Contracts.	37	12,177	11	3,653	4	1,076	9	5,349	4	426	5	7,194			1516	593,301
Intramural ...		29,176		11,141		2,564										907,576
RM&S		12,502		6,465		4,507		12,146		2,672		3,974		5,866		317,393
Control.......																74,614
Construction..																1,000
Total, IRDs...		240,489		176,345		105,030		302,350		32,588		133,000		16,321		7,736,528

National Library of Medicine...	81,983
Office of the Director.........	84,983
Buildings and Facilities.......	88,600
TOTAL, NIH...............	7,992,094

DHHS - National Institutes of Health
FY 1991 PRESIDENT'S BUDGET
(Dollars in thousands)
INCLUDES AIDS

	NCI		NHLBI		NIDR		NIDDK		NINDS		NIAID		NIGMS		NICHD		NEI		NIEHS	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:																				
Noncompeting	2294	$591,434	2057	$518,585	269	$46,453	1534	$317,573	1456	$287,694	1624	$441,578	2381	$432,323	1069	$203,593	889	$136,725	271	$53,753
Admin. supp.	(140)	7,000	(60)	3,676	(3)	160	(40)	1,385	(20)	800	(23)	1,117	(17)	642	(50)	1,712	(30)	1,253	(10)	627
Competing...	815	186,252	718	179,936	103	18,363	495	102,564	405	70,133	580	109,293	819	151,379	362	72,378	218	35,315	89	16,850
Subtot.,RPG.	3109	784,686	2775	702,197	372	64,976	2029	421,522	1861	358,627	2204	551,988	3200	584,344	1431	277,683	1107	173,293	360	71,230
Research Ctrs:																				
Spec/comp...	56	103,004	64	86,295	21	15,936	40	33,766	29	22,247	28	19,865	9	6,950	53	36,914	30	6,613	17	16,550
GCRC........																				
Biotech.....																				
LASPR.......																				
RCMI........												1,834								
Subtotal..	56	103,004	64	86,295	21	15,936	40	33,766	29	22,247	28	21,699	9	6,950	53	36,914	30	6,613	17	16,550
Other Res.:																				
Careers	123	8,323	410	27,753	127	9,156	178	12,211	207	13,971	101	6,057	19	868	113	7,930	24	1,813	22	1,485
Clin. ed....	29	2,942																		
Coop. cl....	189	59,747	14	2,737					1	178					6	1,282	38	13,420		
BRS.........																				
MBRS........		2,801		2,624		175		1,586		215		806	98	32,326		569		319		438
Other.......	200	8,817	112	7,012	57	1,563	60	3,464	59	2,049	67	4,040	84	4,452	63	2,958	64	2,299	13	766
Subtotal..	541	82,630	536	40,126	184	10,894	238	17,261	267	16,413	168	10,903	201	37,646	182	12,739	126	17,851	35	2,689
Total,RGs...	3706	970,320	3375	828,618	577	91,806	2307	472,549	2157	397,287	2400	584,590	3410	628,940	1666	327,336	1263	197,757	412	90,469
Training																				
Indiv.......	178	4,577	225	6,452	29	905	178	4,502	171	4,519	131	3,533	511	14,020	108	2,993	86	2,416	39	947
Instit......	1225	31,216	1399	38,024	186	4,988	717	19,370	357	8,497	539	13,960	3495	71,630	582	13,569	168	4,689	420	9,639
Total, Trng.	1403	35,793	1624	44,476	215	5,893	895	23,872	528	13,016	670	17,493	4006	85,650	690	16,562	254	7,105	459	10,586
R&D Contracts.	394	201,796	242	95,484	20	4,354	52	14,935	42	11,381	172	126,515	7	5,835	124	35,808	51	6,588	182	59,164
Intramural ...		333,219		92,621		28,567		73,295		69,105		115,603		1,099		58,959		26,256		67,840
RM&S		75,993		51,303		9,900		20,698		21,423		42,674		23,970		22,808		9,686		7,733
Control.......		75,459																		
Construction..		1,479																		
Total, IRDs...		1,694,059		1,112,502		140,520		605,349		512,212		886,875		745,494		461,473		247,392		235,792

Research Grants	NIA		NIAMS		NIDCD		DRR		NCNR		NCHGR		FIC		TOTAL	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:																
Noncompeting	453	$106,169	494	$87,610	326	$68,187	4	$787	106	$17,785	117	$34,916			15344	$3,345,165
Admin. supp.	(22)	1,325	(10)	342	(3)	755			(6)	302					(434)	21,096
Competing...	153	38,891	150	30,377	102	22,383			33	6,744	53	17,656			5095	1,058,514
Subtot.,RPG.	606	146,385	644	118,329	428	91,325	4	787	139	24,831	170	52,572			20439	4,424,775
Research Ctrs:																
Spec/comp...	24	26,517	26	21,025	14	13,092			4	1,235	9	35,738			424	445,747
GCRC........							78	116,082							78	116,082
Biotech.....							59	32,087							59	32,087
LASPR.......							53	51,043							53	51,043
RCMI........							20	22,833							20	24,667
Subtotal..	24	26,517	26	21,025	14	13,092	210	222,045	4	1,235	9	35,738			634	669,626
Other Res.:																
Careers	91	7,138	52	3,349	44	2,856	9	561	12	904	12	850			1544	105,225
Clin. ed....															29	2,942
Coop. cl....															248	77,364
BRS.........							810	52,966							810	52,966
MBRS........		494		366		326									98	43,045
Other.......	31	1,646	21	2,012	6	327	129	22,635	4	217	18	1,800	204	10,110	1192	76,167
Subtotal..	122	9,278	73	5,727	50	3,509	948	76,162	16	1,121	30	2,650	204	10,110	3921	357,709
Total,RGs...	752	182,180	743	145,081	492	107,926	1162	298,994	159	27,187	209	90,960	204	10,110	24994	5,452,110
Training																
Indiv.......	31	787	37	1,011	32	859	6	133	151	2,034	75	1,936			1988	51,624
Instit......	354	8,733	188	5,731	90	2,264	69	2,360	94	2,199	149	3,130			10032	239,999
Total, Trng.	385	9,520	225	6,742	122	3,123	75	2,493	245	4,233	224	5,066			12020	291,623
R&D Contracts.	36	11,920	11	3,692	5	2,002	9	5,105	4	359	5	7,971			1356	592,909
Intramural ...		30,558		12,922		4,603				266						914,913
RM&S		14,760		7,643		5,193		12,559		3,082		4,032		6,245		339,702
Control.......																75,459
Construction..																1,479
Total, IRDs...		248,938		176,080		122,847		319,151		35,127		108,029		16,355		7,668,195
National Library of Medicine...																89,916
Office of the Director.........																82,975
Buildings and Facilities.......																88,600
TOTAL, NIH..............																7,929,686

when was the last time the NIH funded so few new and competing grants exclusive of AIDS? Even with AIDS?

Dr. Raub. Not since the early 1980's has NIH funded so few competing research project grants. In 1982, we funded 5,027 competing research project grants.

Mr. Early. The justification indicates that in the aggregate, NIH will fund 123 more awards than in FY 1990, correct? Doctor, if we exclude the increase in AIDS and genome grants, how many more grants will you fund for all other research areas that NIH supports?

Dr. Raub. Excluding grants for AIDS and the Human Genome Program, NIH will fund 19,417 grants in FY 1991, a decrease of 21 from the FY 1990 level of 19,430.

Mr. Early. To what payline or percentile will you fund under the FY 1991 request, and how does this compare to FY 1990 and FY 1989?

Dr. Raub. We estimate that we will pay to the 19th percentile in FY 1991 and to the 18th percentile in FY 1990. We paid to the 25th percentile in FY 1989.

Mr. Early. With the exception of this year, would you say this is the lowest benchmark to which NIH has paid?

Dr. Raub. Fiscal year 1989 was the first year the percentile paylines were used NIH-wide. We therefore do not have enough historical data to make a categorical statement of that type. The most germane funding indicator, the award rate, is estimated to be 25 percent in FY 1991, the lowest rate in over ten years with the exception of the FY 1990 rate of 24 percent.

Mr. Early. What is the range of percentile paylines?

Dr. Raub. Estimates for percentile paylines for FY 1991 range from 11 for the National Center for Nursing Research to 31 for the National Eye Institute.

Mr. Early. Can you derive a priority score from the percentile score for us?

Dr. Raub. The relationship varies from review group to review group and cannot be described by a formula or otherwise predicted.

Mr. Early. What percentage of new and competing grants will you fund under the request and how does this compare to FY 1990 and FY 1989?

Dr. Raub. Our award rate is estimated to be 25 percent for FY 1991 compared to an estimate of 24 percent for FY 1990 and an actual of 29.4 percent for FY 1989.

Mr. Early. When was the last time you had such a low award rate?

Dr. Raub. The award rate estimates for fiscal years 1990 and 1991 are the lowest rates in our history.

Mr. Early. What is the percentage range?

Dr. Raub. The estimated percentages for FY 1991 award rates range from 12 percent for the National Center for Nursing Research to 38 percent for the National Eye Institute.

Mr. Early. In general, how does this compare to past years?

Dr. Raub. The estimated percentages for FY 1990 award rates range from 19 percent for the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Center for Nursing Research to 42 percent for the National Eye Institute.

Mr. Early. Doctor, of the number of new and competing grants that could be funded (exclusive of AIDS), how many new as opposed to competing renewals do you anticipate funding?

Dr. Raub. Of the 5,095 competing grants in the FY 1991 Budget Request, including AIDS, 2,246 are competing renewals, 2,773 are new, and 76 are supplementals. Comparable figures excluding AIDS grants are not readily available.

Mr. Early. Doctor, of the grants in non-competing status in FY 1990, how many will revert to competing status in FY 1991?

Dr. Raub. Of the FY 1990 noncompeting grants, we estimate that approximately 5,000 will convert to competing status in FY 1991.

Mr. Early. What are the prospects of a competing renewal being funded under your FY 1991 request? What about new grants?

Dr. Raub. We estimate that a competing renewal has an approximately 40 percent chance of being renewed. A new grant has an approximately 20 percent chance of being funded.

Mr. Early. Doctor, would you care to speculate on what will happen to research efforts of competing renewals that are not funded? Won't it be difficult to hold those research teams together?

Dr. Raub. In certain instances, the research efforts of a competing grant that successfully competes but does not get funded are terminated. These grants may be extended with or without funds to conclude in an orderly manner. Some investigators with an approved but unfunded renewal application will submit an amendment in hopes that their grant will be funded in the next fiscal year.

Some investigators will also seek support from other sources. Investigators are generally informed of their funding status several months prior to any termination of funding.

BRSG PROGRAM

Mr. Early. One of the common uses of BRSG funds is to provide interim funding between grant supported projects, isn't it? Since you are proposing such a substantial reduction in the BRSG program, isn't it true that this source of interim funding will not be available?

Dr. Raub. The BRSG program provides flexible funds on a formula basis to institutions to support biomedical research needs not served by other support programs. BRSG funds are used to provide central shared resources; to explore new and unorthodox research ideas and techniques; and to provide support for new investigators and emerging technologies. We recognize these as valuable contributions, but in order to devote the maximum amount for the very highest priority activities, we reduced the level of support for this program. It is hoped that at the FY 1991 request level of $17.7 million, the BRSG program can continue to provide a reasonable level of support for interim funding needs, as well as for the other activities these funds support.

QUALITY OF RESEARCH APPLICATIONS

Mr. Early. How would you characterize the quality of research applications?

Dr. Raub. The quality of research applications and new ideas continues to generate the dynamic characteristics of the biomedical research enterprise as witnessed by the burgeoning fields of the neurosciences, biotechnology and the new discoveries that will enable us to map the human genome.

RESEARCH PROJECT GRANTS

Mr. Early. Doctor, how many new and competing grants did NIH propose to fund in FY 1991? What about the total number?

Dr. Raub. In the 1991 request to the PHS, NIH proposed to fund 8,863 competing awards and 24,694 total awards, including AIDS.

Mr. Early. Please provide for the record a table displaying by Institute the number of new and competing grants, the paylines and/or percentiles, and the award rates for FY 1986 through FY 1990 and the FY 1991 budget request.

Dr. Raub. The table displaying new and competing grants by Institute is on the following page.

Mr. Early. Doctor, of the 13 Institutes, how many will have downward negotiations of 10 percent or more for noncompeting awards? For competing awards?

Dr. Raub. The number of institutes having downwa negotiations of 10 percent or more is 12 for noncompeting awards and 13 for competing awards.

INCLUDES AIDS

DHHS-National Institutes of Health
COMPETING RESEARCH PROJECT GRANTS-APPLICATIONS FUNDED

(Dollars in thousands)

	FY 1989 ACTUAL					FY 1990 ESTIMATE					FY 1991 ESTIMATE				
	NUMBER	AMOUNT	PERCENTILE PAYLINES	AWARD RATE	AVERAGE COST	NUMBER	AMOUNT	PERCENTILE PAYLINES	AWARD RATE	AVERAGE COST	NUMBER	AMOUNT	PERCENTILE PAYLINES	AWARD RATE	AVERAGE COST
NCI	728	$158,775	22.6	26.7%	$218.1	766	$183,454	18	27.6%	$239.5	815	$186,252	21	30.2%	$228.5
NHLBI	698	149,689	23.8	27.9%	214.5	601	145,513	14	22.0%	242.1	718	179,936	16	25.8%	250.6
NIDR	109	17,516	24.2	26.6%	160.7	90	15,172	12	20.5%	168.6	103	18,363	14	21.5%	178.3
NIDDK	504	92,455	24.6	27.6%	183.4	420	82,545	17	22.4%	196.5	495	102,564	20	25.6%	207.2
NINDS	493	83,761	30.1	33.7%	169.9	471	84,242	17	31.4%	178.9	405	70,133	19	26.6%	173.2
NIAID	652	113,767	27.3	31.9%	174.5	476	99,215	16	22.0%	208.4	580	109,293	14	24.4%	188.4
NIGMS	788	126,965	23.0	29.1%	161.1	637	112,736	14	23.1%	177.0	819	151,379	18	26.1%	184.8
NICHD	433	71,557	21.1	26.5%	165.3	323	59,812	14	19.8%	185.2	362	72,378	16	22.5%	199.9
NEI	310	45,021	39.5	46.8%	145.2	247	38,629	34	41.6%	156.4	218	35,315	31	37.7%	162.0
NIEHS	100	18,124	30.3	27.5%	181.2	99	18,375	25	23.7%	185.6	89	16,850	22	21.3%	189.3
NIA	194	38,948	29.8	25.6%	200.8	156	34,956	23	19.4%	224.1	153	38,891	21	17.0%	254.2
NIAMS	185	30,544	20.7	28.2%	165.1	135	22,511	14	18.5%	166.7	150	30,377	14	19.3%	202.5
NIDCD	97	16,973	27.9	38.2%	175.0	113	21,796	28	37.8%	192.9	102	22,383	25	33.4%	219.4
NCNR	50	7,902	25.8	25.1%	158.0	45	8,480	18	18.8%	188.4	33	6,744	11	11.6%	204.4
NCHGR	41	10,436	39.3	36.3%	254.5	50	15160	26	27.0%	303.2	53	17,656	30	28.6%	333.1
DRR	--	---	--	--	---	4	749	--	8.0%	187.3	--	---	--	--	---
TOTAL NIH	5382	982,433		29.4%	182.5	4633	943,345		24.1%	203.6	5095	1,058,514		25.4%	207.8

NOTES: Paylines for FY 1986 - 1988 actuals represent the 90th percentile priority score, based on the number of funded research projects. For FY 1989 - 1991, "percentile paylines" are shown.

The Arthritis Institute (NIAMS) was established in 1986, prior year data contained under the parent Institute, NIDDK (formerly NIADDK). The National Center for Nursing Research (NCNR) was formerly under the administration of HRSA. The National Institute on Deafness and Communicative Disorders was established in FY 1988, prior year data contained under parent Institute, NINDS (formerly NINCDS). The National Center for Human Genome Research (NCHGR) was established in FY 1990.

1/ NHLBI and NICHD used percentiles for making funding decisions and the priority scores shown are derived from the percentile score listings in an analogous manner.

INCLUDES AIDS

DHHS-National Institutes of Health
COMPETING RESEARCH PROJECT GRANTS-APPLICATIONS FUNDED

(Dollars in thousands)

	FY 1986 ACTUAL 1/					FY 1987 ACTUAL 1/					FY 1988 ACTUAL 1/				
	NUMBER	AMOUNT	PAYLINES	AWARD RATE	AVERAGE COST	NUMBER	AMOUNT	PAYLINES	AWARD RATE	AVERAGE COST	NUMBER	AMOUNT	PAYLINES	AWARD RATE	AVERAGE COST
NCI	953	$163,483	165	34.0%	$171.5	1061	$218,193	165	38.6%	$205.6	979	$205,378	158	36.7%	$209.8
NHLBI	886	155,972	156	35.7	176.0	966	178,420	157	35.7	184.7	851	175,664	155	34.0	206.4
NIDR	151	18,357	187	40.3	121.6	130	20,117	186	33.3	154.7	114	18,494	194	28.4	162.2
NIDDK	637	93,729	165	35.4	147.1	686	114,630	169	40.3	167.1	594	98,479	170	33.9	165.8
NINCDS	643	94,295	159	37.8	146.6	697	116,836	169	43.4	167.6	596	90,734	170	42.0	152.2
NIAID	549	80,613	158	34.7	146.8	641	129,627	181	36.8	202.2	636	124,061	169	33.3	195.1
NIGMS	981	131,212	160	42.6	133.8	857	135,612	154	39.5	158.2	1044	167,394	151	39.9	160.3
NICHD	490	65,038	161	27.1	132.7	545	77,938	164	35.6	143.0	450	69,074	156	27.0	153.5
NEI	362	45,735	192	51.0	126.3	313	43,878	187	53.4	140.2	277	39,595	219	48.3	142.9
NIEHS	107	16,195	181	29.4	151.4	129	20,249	175	32.3	157.0	114	20,596	166	31.1	180.7
NIA	205	33,253	189	31.1	162.2	201	37,780	198	34.3	188.0	214	37,785	182	30.0	176.6
NIAMS	199	26,371	155	33.1	132.5	179	28,701	147	30.8	160.3	188	27,529	149	28.0	146.4
NIDCD	--	---	--	--	---	--	---	--	--	---	104	16176	170	42.1	155.5
NCNR	48	6,021	223	77.4	125.4	48	7,855	197	61.5	163.6	52	7,579	174	46.4	145.8
TOTAL NIH	6211	930,274	171	36.1	149.8	6453	1,129,836	174	38.3	175.1	6213	1,098,538	170	35.3	176.8

NOTES: Paylines for FY 1986 - 1988 actuals represent the 90th percentile priority score, based on the number of funded research projects. For FY 1989 - 1991, "percentile paylines" are shown.

The Arthritis Institute (NIAMS) was established in 1986, prior year data contained under the parent Institute, NIDDK (formerly NIADDK). The National Center for Nursing Research (NCNR) was formerly under the administration of HRSA. The National Institute on Deafness and Communicative Disorders was established in FY 1988, prior year data contained under parent Institute, NINDS (formerly NINCDS). The National Center for Human Genome Research (NCHGR) was established in FY 1990.

1/ NHLBI and NICHD used percentiles for making funding decisions and the priority scores shown are derived from the percentile score listings in an analogous manner.

Mr. Early. What is the average downward negotiations for noncompeting grants over the last five years, including this FY 1991 budget request?

Dr. Raub. Over the last five years, the average downward negotiations rate for noncompeting awards is 8.1 percent.

Mr. Early. What is it for competing grants?

Dr. Raub. Over the last five years for competing awards, the average downward negotiation rate is 11.1 percent.

Mr. Early. Doctor, what does a grant budget/award consist of? What gets cut out when downward negotiations are applied?

Dr. Raub. A typical budget for the conduct of a research project grant consists of amounts for: salaries of the principal investigator and other personnel engaged directly in the project; fringe benefits related to those salaries; equipment; supplies; travel; and other expenses, such as publication costs, computer charges, and equipment maintenance. Depending on the particular needs of the project, other direct costs that may be required are those for consultants, patient care, alterations and renovations, and arrangements with a collaborative institution. Associated indirect costs according to the negotiated rate(s) of the grantee organization are provided also.

Generally, all direct cost budget categories (except equipment) are reduced proportionately upon application of downward negotiations. Staff attempt to apply these reductions in a reasonable fashion to maintain the integrity of the approved project.

Mr. Early. Are we continuing to discourage more adventurous scientists from taking risks? Are we discouraging innovative ideas? Are study sections becoming more conservative--less willing to take a risk on an innovative or unusual proposal?

Dr. Raub. Yes, I believe that when the funds for research project grants are tight there is a tendency to be more conservative and not take risks. I also believe that the study section members are concerned with large downward negotiations.

Mr. Early. Doctor, what do the study sections think of another year of large downward negotiations?

Dr. Raub. Let me reemphasize that the study sections are the first part of the NIH dual review system, and as such are responsible for the scientific and technical merit review of applications for grant support--not for their funding. Nevertheless, large downward negotiations impact upon them in several ways.

First, the study sections do address the appropriateness of the applicant's budgetary request and are instructed to modify the budget as they deem appropriate in order to provide the applicant with the resources they believe are adequate for the conduct of the research proposed. Thus, the reviewers believe that additional paring of the budget would significantly impair the applicant's ability to conduct the research as proposed.

A further difficulty can occur when the renewal application is reviewed several years later. Because of such administrative budgetary reductions, the investigator may not have been able to accomplish all of what the study section approved during the previous review, and confusion as to what should be an appropriate amount of progress in the investigator's research may arise.

Finally, most study section members are themselves grantees and thus suffer from the same degree of pessimism as their colleagues.

Mr. Early. As scores or paylines become lower, doesn't this complicate things?

Dr. Raub. Yes, funding decisions do become much more difficult as the quality of the projects improve.

Mr. Early. Are downward negotiations assumed for mechanisms other than research grant awards?

Dr. Raub. Yes. The FY 1991 President's budget assumes downward negotiations in the research centers mechanism of about 17.4 percent at the aggregate NIH level. The reductions at the institute level range from 2.3 percent to 30 percent. There are also downward negotiations in cooperative clinical research grants of approximately 30 percent.

Mr. Early. How much do you expect to "save" in FY 1991 as a result of downward negotiations?

Dr. Raub. Approximately $628.8 million would be saved as a result of the downward negotiations proposed in the FY 1991 budget for research project grants (after historical downward negotiations), research centers, and cooperative clinical research grants.

Mr. Early. Doctor, will these downward negotiations be applied to all research grants and centers, or are you making any exceptions?

Dr. Raub. The rates of downward negotiations are overall rates and will not be applied across-the-board to all grant awards. The amount negotiated will be individually determined for each award. Some awards may be reduced by higher amounts while a few awards may experience little or no reductions.

Mr. Early. Please provide for the record a breakdown for each Institute, by mechanism, of the percentage reduction in direct costs, and the associated savings.

Dr. Raub. The following table displays the percentage reductions and associated savings.

DHHS - NATIONAL INSTITUTES OF HEALTH

FY 1991 PERCENT REDUCTIONS AND DOLLAR SAVINGS RESULTING FROM DOWNWARD NEGOTIATIONS

BY APPROPRIATION

(Dollars in thousands)

INCLUDES AIDS

	COMPETING RPGS		NONCOMPETING RPGS		RESEARCH CENTERS		OTHER RESEARCH GRANTS		TOTAL SAVINGS
	% RED.	SAVINGS	% RED.	SAVINGS	% RED.	SAVINGS	% RED.	SAVINGS	
NCI......	20.0	$46.664	4.0	$24.643	2.3	$2.438	30.0	$6.518	$80.263
NHLBI....	13.9	29.029	11.0	63.975	24.4	27.801	---	---	120.805
NIDR.....	15.0	3.241	12.0	6.335	16.3	3.111	---	---	12.687
NIDDK....	10.9	12.501	10.9	38.704	30.0	14.471	---	---	65.676
NINDS....	25.1	23.541	12.0	39.253	18.0	4.875	---	---	67.669
NIAID....	10.0	12.144	10.0	49.065	21.5	5.934	---	---	67.143
NIGMS....	12.7	22.037	12.7	62.735	6.9	514	---	---	85.296
NICHD....	12.0	9.889	15.5	37.345	21.6	10.183	---	---	57.417
NEI......	10.3	4.038	10.3	15.743	30.0	2.834	---	---	22.615
NIEHS....	7.3	1.324	5.0	2.835	13.4	2.563	---	---	6.722
NIA......	10.4	4.513	10.5	12.499	21.4	7.215	---	---	24.227
NIAMS....	11.5	3.946	11.8	11.771	17.0	4.306	---	---	20.023
NIDCD....	8.0	1.937	9.0	6.750	17.5	2.775	---	---	11.462
DRR......	---	---	10.1	88	17.7	47.842	---	---	47.930
NCNR.....	16.5	1.330	17.8	3.859	9.3	126	---	---	5.315
NCHGR....	10.4	2.060	5.0	1.833	10.0	3.971	---	---	7.864
TOTAL	14.4	178.194	10.0	377.433	17.4	140.959	30.0	6.518	703.104

NOTE: Savings in research project grants from downward negotiations shown on this table represent the difference between estimated council recommended levels and award amounts and therefore include savings that would occur through normal historical downward negotiations of one percent for noncompeting and three percent for competing grants. Savings as a result of budget constraints only would therefore be less than the amounts shown.

CLINICAL TRIALS

Mr. Early. Will you be able to continue the trials now underway at their planned levels with the FY 1991 request? Are there any that will have to be terminated or curtailed?

Dr. Raub. All ongoing clinical trials will be continued under the FY 1991 request, some at levels less than originally planned. Also, some planned expansions of ongoing trials will not be supported. Because of negotiated reductions, those trials funded through the research project grant and research center mechanisms will be funded at reduced levels.

Although no terminations are anticipated in FY 1991, some curtailment of ongoing trials may be necessary. For example, fewer patients may be recruited and some aspects of the trials may have to be modified.

Mr. Early. Are there any clinical trials that could be undertaken in FY 1991 if additional resources are available?

Dr. Raub. Yes, the National Institutes of Health has numerous clinical trials that could be undertaken in FY 1991 if funds were available.

Mr. Early. Please provide a list of these for the record, along with a brief description of the trial, the duration of the trial, the first year cost and the estimated total cost of the trial.

Dr. Raub. Following is a list of major unfunded clinical trials that total $256,036,000.

SEQUESTRATION

Mr. Early. Were you able to regroup the amount sequestered in your FY 1991 base? If not, what is the sequester amount that is absorbed? Is it the same as the FY 1990 dollar amount or is it greater?

Dr. Raub. No. The FY 1991 request was developed based on the FY 1990 appropriations after sequestration. The amount absorbed in FY 1991 would be the FY 1990 sequester amount of $96.6 million plus any increase that may have been built in for inflation.

PAY RAISE

Mr. Early. What is the total cost of the January 1990 and SES Pay raises for NIH and how will these costs be covered?

Dr. Raub. The cost of the January 1990 pay raise is estimated at $23.8 million, including the SES pay raise estimated at $631,000. In accordance with the FY 1990 Appropriations Act, these costs were absorbed within the total levels appropriated to the NIH. This was achieved primarily by redistributing funds from research project grants and by reducing or delaying the purchases of supplies and equipment.

NATIONAL INSTITUTES OF HEALTH

MAJOR NEW CLINICAL TRIALS READY TO BEGIN IN FY 1991 IF FUNDS WERE AVAILABLE
(Dollars in thousands)

(Non-AIDS)

NCI	First Year Cost	Total Projected Cost	Duration (years)
TREATMENT/DETECTION/DIAGNOSIS:			
Trans-retinoic Acid and Other Biologicals in Children with Leukemia and Selected Solid Tumors	$500	$1,500	3
Early Empirical Antifungal Therapy in Febrile Neutropenic Patients	300	900	2-3
GM-CSF for the Management of Patients with Fever and Neutropenia	2,000	6,000	3
Purigenic Receptor Agonist in Prostate Cancer	200	600	2-3
Attainment of Optimal Patient Accrual Rates in Contract-Supported Clinical Trials	2,700	10,700	5
Clinical Trials of Novel Therapeutic Agents (oligodeoxynucleotides and immuno-toxin conjugates)	1,500 2,000	3,000 6,000	2 3
Trial of Anti-growth Factor Therapy in Multiple Myeloma, Malignant Melanoma, Ovary and Prostate, Including Use of Suramin and Suramin Analogs	1,125 2,000	2,250 6,000	2 3
Increased Accrual of Minority and Other Underserved Populations in Clinical Trials	4,000	12,000	3
Increased Accrual into High Priority National Clinical Trials, Including Patients Over Age 65	7,000	21,000	3
Expansion of Adoptive Immunotherapy/combination Cytokine Trials/Gene Transfer Studies	1,000 1,500	2,000 4,500	2 3
Evaluation of the Role of Suppressor Oncogenes on Lung, Colon and Breast Cancers	1,000	2,000	2
Trial of Photodynamic Therapy in Refractory Malignancies (including ovarian/bladder cancers and mesothelioma)	75 775	150 2,325	2 3
Expansion and Follow-up of Adjuvant Therapy Trials in Breast, Colon, and Rectal Cancers	2,000	6,000	3
Expanded Correlation in Clinical Trials with Laboratory/Basic Science Studies	2,000	6,000	3
Bone Marrow Transplantation Initiatives	1,000	3,000	3
Development of Diagnostic Imaging to Study Perfusion	600	1,800	3
Digitalization of Chest Radiography	450	1,350	3

UNFUNDED CLINICAL TRIALS: FY 1991 (Non-AIDS)

NCI (Continued)	First Year Cost	Total Projected Cost	Duration (years)
Radiolabelled MoAB Studies	$1,000	$3,000	3
Synthesis of Compounds for Boron Neutron Capture Therapy	475	1,425	3
Imaging of Bone Marrow Tumors	500	1,500	3
Clinical PET Studies of Brain Tumor Metabolism	900	2,700	3
Use of Fludarabine for Treatment of Low Grade Lymphomas	400	800	2
Clinical Application of Monoclonal Antibodies in Diagnostic Studies (Expansion)	1,000	2,000	2
PREVENTION & CONTROL:			
Funding of 8 Additional Minority-based CCOPS, Increasing Minority Patient Accrual	1,200	3,600	3
Prevention Clinical Trial within CCOPS/Groups Network	4,000	12,000	5
Finland Study - Additional Resources for Serum Bank	934	934	1
Fund Additional CCOPS to Optimize Patient Accrual	8,400	25,200	3
Women's Nutrition Health Trial	15,000	150,000	10
CORE SUPPORT FOR CLINICAL RESEARCH:			
Increased Support for Clinical/Comprehensive Cancer Centers	33,000	165,000	5
Total, NCI	100,534	467,234	

NHLBI	First Year Cost	Total Projected Cost	Duration (years)
Child and Adolescent Trial for Cardiovascular Health	6,000	42,000	9
Coronary Heart Disease in High Risk Hypertensives	2,100	90,000	12
Peripheral Vascular Disease	1,000	58,000	11
Effect of Digitalis on Survival in Patients with Coronary Heart Failure	200	6,500	7
Hyperglycemia as a Risk Factor for Cardiovascular Disease	777	3,327	5
Antiarrhythics and Beta-Blockers Study	2,000	45,000	8
Management of Elevated Blood Pressure in Children	2,300	24,000	8
Treatment of Idiopathic Fibrotic Lung Disease	1,000	30,000	6
Membrane-Active Agents to Prevent Sickle Cell Disease	500	3,000	3
Transfusion Therapy for Prevention of Recurrence of Stroke in Sickle Cell Disease	750	9,668	8
Sleep Apnea Intervention Trial	1,782	13,036	13
Childhood Asthma Management Program (CAMP)	875	40,000	8
Total, NHLBI	19,284	364,531	

UNFUNDED CLINICAL TRIALS: FY 1991 (Non-AIDS)

	First Year Cost	Total Projected Cost	Duration (years)
NIDR			
Evaluation of Exposure to Fluoride in Non-fluoridated Communities	$500	$1,000	2
Evaluation of Various Modalities for Preventing Caries, Improving Periodontal Health, Retaining Permanent Teeth, and Practicing Self-care in 'Special Patient' Populations	1,500	6,000	4
Evaluation of Various Modalities for Preventing Caries, Improving Periodontal Health, Retaining Permanent Teeth, and Practicing Self-care in Patients with 'Orphan Diseases'	1,500	6,000	4
Evaluating New Clinical Approaches to Treating the Loss of Alveolar Bone and of Periodontal Attachment through Guided Tissue Regeneration and Osteogenin	1,500	5,000	4
Prevention and Reduction of Oral Complications from Cancer Chemotherapy and Radiation	1,000	3,000	4
Evaluating the Effects of Various Treatments to Suppress Recurrence of Herpesvirus	1,000	3,000	4
Effect of Drug Pretreatment of Individuals at Risk for Oral Cancer	500	1,500	4
Effects of Drug Therapy on Recurrent Oral Cancer	500	3,000	6
Clinical Evaluation of Sealants, Xylitol, Chlorhexidine, and Various Fluoride Modalities for Caries Prevention in High-risk Populations	1,500	3,000	3
Multi-institutional Clinical Trial of Single- and Multi-tooth Dental Implants	1,500	6,000	4
Evaluation of Criteria for Replacement of Dental Restorations	400	2,000	6
Analgesic and Biochemical Responses to Peripheral Opiates in Patients with Dental Pain	150	300	2
Evaluating Non-invasive Treatment for Temporomandibular Disorders	750	2,500	4
Rehabilitation of Dysphagic Patients	500	2,000	4
Effect of Periodontal Treatment on Insulin Requirements of Patients with Diabetic Periodontitis	500	1,500	4
Assessment of New Dental Biomaterials (e.g., bonding materials, dental cement, and root canal materials)	1,000	3,000	4
Orthognathic Surgery Clinical Trials	600	2,400	4
Evaluation of Various Prostheses for Orofacial Reconstruction	500	2,000	4
Total, NIDR	15,400	53,200	

UNFUNDED CLINICAL TRIALS: FY 1991 (Non-AIDS)

NIDDK	First Year Cost	Total Projected Cost	Duration (years)
Diet and Exercise in the Prevention and Treatment of Noninsulin-dependent Diabetes Mellitus	$1,500	$6,000	5
Clinical Study of Gallstone Recurrence Following Extracorporeal Shock-Wave Lithotripsy	1,000	6,000	6
Use of Recombinant Human Erythropoietin in Adult and Pediatric Patients with Renal Failure	1,000	5,750	5
Clinical Trials in the Treatment of Primary Biliary Cirrhosis (PBC)	2,000	14,000	8
Comparison of Therapeutic Modalities in the Treatment of Interstitial Cystitis	1,000	5,750	5
Comparison of Surgery Versus Medical Follow-up in Asymptomatic Hyperparathyroidism	1,000	10,000	10
Clinical Trial of Prevention and Therapy of Hypertensive Renal Disease in Blacks	2,000	11,500	5
Enzyme Replacement Therapy in Inherited Metabolic Diseases	1,000	6,500	5
Immunosuppressants in Crohn's Disease	1,500	8,500	5
Effective Weight Loss Strategies for Obese Diabetics in High Risk Minority Populations	1,500	6,000	5
Liver Transplantation Trials Using Alpha Interferon, PGE-1 in Severe Viral Hepatitis; Mabs to Prevent Reinfection in Hepatitis; and Salmon Calcitonin After Liver Transplantation in PBC Patients	1,200	2,500	2
The Efficacy of Alternative Therapies for the Treatment of Symptomatic Benign Prostatic Hyperplasia	1,500	9,000	5
Peptic Ulcers: Role of Helicobacter pylori	3,000	8,000	7
The Long-Term Effects of Extracorporeal Shock-Wave Lithotripsy on the Kidney and Other Organs	1,500	8,000	5
Immunotherapy for pre-Type I Diabetics	1,000	5,000	5
Comparison of Amino Acid and Ketoacid Analogues to Essential Amino Acids as Nutritional Supplements for Protein Restricted Diets	2,000	11,500	5
Comparison of Radioiodine Versus Antithyroid Drug Therapy for Graves Disease	750	8,000	10
Effect of Diet on Lipid Levels in Diabetic Patients	800	3,000	3
Total, NIDDK	25,250	135,000	

UNFUNDED CLINICAL TRIALS: FY 1991 (Non-AIDS)

	First Year Cost	Total Projected Cost	Duration (years)
NINDS			
Pegolated Superoxide Dismutase (PEG-SOD) in the Treatment of Traumatic Head Injury	$1,000	$5,000	5
National Acute Spinal Cord Injury Study III	1,000	5,000	5
TRH (thyroxin releasing hormone) in the Treatment of Traumatic Spinal Cord Injury	750	3,750	5
Monoclonal Antibody Treatment of Multiple Sclerosis	500	1,500	3
Efficacy Trial of a Calcium Channel Blocker in Patients with Partial Seizures	500	1,000	3
Efficacy Trial of an Anticonvulsant in Patients with Partial Seizures	300	750	3
Total, NINDS	4,050	17,000	
NIAID			
Cholera Vaccine	1,500	6,000	4
Pneumococcal Polysaccharide Vaccine	200	200	1
Prophylactic Therapy of Neonatal Herpes	921	4,986	5
Oral Rotavirus Vaccine	1,000	2,000	2
Immunotherapy of Recurrent Genital Herpes	216	300	2
Total, NIAID	3,837	13,486	
NICHD			
Collaborative Multicenter Clinical Trial of Hyperventilation vs. Minimal Ventilation in Pts with Primary Pulmonary Hypertension of Newborn	1,500	3,000	2
Cooperative Multi-center Reproductive Medicine Network	2,000	8,000	4
Use of Ambulatory Tocodynamometry to Prevent Preterm Birth	2,500	8,000	3
Testing of Disposable Spermicide Releasing Barrier Devices	350	1,100	3
Event Recording of Apnea & Bradycardia in High-Risk Infants	750	2,000	3
Prognostic Clinical Tests for SIDS	3,500	18,000	5
Iron Deficiency Anemia and Infant Behavior: A Prevention Trial	220	660	3
Interventions to Improve African-American Pregnancy Outcomes	1,200	6,000	5
Calcium Supplementation in the Prevention of Pregnancy-Induced Hypertension and Preterm Birth	300	4,300	6
Total, NICHD	12,320	51,060	

UNFUNDED CLINICAL TRIALS: FY 1991 (Non-AIDS)

	First Year Cost	Total Projected Cost	Duration (years)
NEI			
Effect of Light Reduction on Retinopathy of Prematurity	$2,000	$10,800	5
Therapeutic Oxygen in Retinopathy of Prematurity	1,000	5,400	5
Advanced Retinopathy of Prematurity Study	3,000	16,300	5
Contact Lens Evaluation in Keratoconus	1,000	5,400	5
Barbados Glaucoma Treatment Trial	1,000	5,400	5
Long-term Follow-Up of PERK Patients	500	2,700	5
Quality of Life Assessment Following Glaucoma Treatment	1,000	5,400	5
Treatment of Congenital Esotropia	4,000	21,700	5
Efficacy of IOP Lowering in Ocular Hypertensives	5,000	27,100	5
Total, NEI	18,500	100,200	
NIA			
Clinical Trial of Acetylcarnitine as a Treatment for Alzheimer's Disease	4,500	20,000	4
Clinical Trial of Nerve Growth Factor as a Treatment for Alzheimer's Disease	5,500	22,000	4
Clinical Trial of Interventions to Decrease Aggressive/Agitated Behavior in AD Nursing Home Residents	650	4,200	5
Clinical Trial of Psychotrophic Management of Behavioral and Psychotic Symptoms in AD	650	4,200	5
Clinical Trial to Reduce the Burden of Care in AD	2,500	15,000	5
Clinical Trial of Cognitive Interventions to Improve Intellectual Functioning	1,500	10,000	10
Clinical Trial of Psychosocial Interventions for Improving Work Environments for Older Workers	1,000	5,000	3
Total, NIA	16,300	80,400	
NIAMS			
Treatment of the Late Stages of Lyme Disease	500	1,100	2
Treatment of Erythema Migrans	1,000	2,100	2
Safety and Efficacy of Human Calcitonin in the Treatment of Osteoporosis	1,000	2,280	2

UNFUNDED CLINICAL TRIALS: FY 1991 (Non-AIDS)

NIAMS (Continued)	First Year Cost	Total Projected Cost	Duration (years)
Safety and Efficacy of Bisphosphonates in the Treatment of Osteoporosis	$1,000	$2,280	2
Early and Aggressive Combination Therapies for Rheumatoid Arthritis	600	9,000	5
Safety and Efficacy of 4-hydroxyphenylretinamide in Patients with Rheumatoid Arthritis	1,500	5,400	3
Epidermal Growth Factor in the Treatment of Epidermolysis Bullosa	200	600	3
Efficacy of 13-cis Retinoic Acid and Other Retinoid Derivatives in the Treatment of Keratinizing Disorders	1,000	3,000	3
Use of Retinoids in the Treatment of Psoriatic Arthritis	500	1,025	2
Investigations Using the Cooperative Systemic Study of Rheumatic Diseases Serum Bank	150	450	3
Olive Oil in the Prevention of Rheumatoid Arthritis	200	1,000	5
Total, NIAMS	7,650	28,235	
NIDCD			
Evaluation of Thyroplasty for Treating Vocal Fold Movement Disorder	100	500	5
Drug Treatment of Tinnitus	1,500	7,500	5
Drug Protection Against Noise-induced Hearing Loss	300	600	2
Prevention of Central Auditory Changes Following Peripheral Hearing Impairment	300	600	2
Use of Steroids and Surgery for Treatment of Olfactory Defects	800	4,000	5
Intraoperative Cranial Nerve Monitoring as a Means of Preventing Sensory Deficits Following Neurosurgery	500	1,500	3
Total, NIDCD	3,500	14,700	
Total, NIH, Major New in FY 1991 Unfunded (Non-AIDS)	226,625	1,325,046	

MAJOR NEW CLINICAL TRIALS READY TO BEGIN IN FY 1991 IF FUNDS WERE AVAILABLE
(Dollars in thousands)

(AIDS)

	First Year Cost	Total Projected Cost	Duration (years)
NCI			
Adoptive Immunotherapy in Children with AIDS (Expansion)	$1,000	$5,000	3
B1 Antibody for Treatment of B-Cell Lymphoma Associated with AIDS (Expansion)	500	3,000	3
Clinical Trials of Novel Therapeutic Agents (immunoconjugates, oligonucleotides, nucleoside analogs)	4,200	8,400	2
	7,000	14,000	2
Trial of Anti-growth Factor Therapy	375	750	2
Trial of Photodynamic Therapy in Kaposi's Sarcoma	225	450	2
	275	825	3
Development of Diagnostic Imaging Strategies in AIDS	800	2,400	3
Digitalization of Chest Radiography	150	450	3
Treatment of High Grade Lymphomas and AIDS	200	400	2
Total, NCI	14,725	35,675	
NIDR			
Evaluation of the Use of Genetic Probes of Gingival Crevicular Fluid for the Early Detection of HIV Infection	750	2,200	3
Salivary Gland Secretions in HIV Infection	250	250	1
Evaluation of Mucosal Biopsies from AIDS Patients for Candidiasis	250	750	3
Salivary and Intestinal Fluid IgA Response in Patients with AIDS	300	900	3
Development and Testing of Methods to be Used for Epidemiological Studies of Human Papillomaviruses in the Oral Cavity	100	200	3
Total, NIDR	1,650	4,300	
NIAID			
DDI/Foscarnet/Gancyclovir	1,718	3,436	2
DDI/Interferon	1,718	1,718	1
Total, NIAID	3,436	5,154	

UNFUNDED CLINICAL TRIALS: FY 1991 (AIDS)

	First Year Cost	Total Projected Cost	Duration (years)
NICHD			
Phase II Trial of AZT in Newborns born to HIV-Infected Mothers	$2,500	$7,500	3
Phase II trial of AZT Administered to HIV-Infected Women in the Third Trimester of Pregnancy	3,500	10,500	3
Total, NICHD	6,000	18,000	
NEI			
CMV Retinitis Risk Factor	3,100	24,500	7
Total, NEI	3,100	24,500	
NIAMS			
AZT in the Treatment of Skin Diseases in HIV-Positive Individuals	500	2,500	5
Total, NIAMS	500	2,500	
Total, NIH, Major New in FY 1991 Unfunded (AIDS)	29,411	90,129	
TOTAL, NIH, Major New in FY 1991 Unfunded (Non-AIDS and AIDS)	256,036	1,415,175	

Mr. Early. If this cost did not have to be absorbed, how would NIH have used these funds?

Dr. Raub. If the pay raise did not have to be absorbed, these funds would be available to reduce the downward negotiations and to provide for additional research project grants. In addition, more funds would be available for equipment and supply purchases for the intramural research programs, additional site visits to grantees and contractors and increased attendance at scientific meetings and symposia.

Mr. Early. Does the FY 1991 budget request allow for the full cost of the 1990 pay raises or were you required to absorb part of this cost in FY 1991?

Dr. Raub. That portion of the pay raise cost occurring in FY 1990 will be absorbed; that portion of the pay raise annualized into FY 1991 is covered by an increase in the FY 1991 President's budget.

Mr. Early. What is the cost of the proposed January 1991 pay raise and the next phase of the SES increase for NIH? How much is included in your FY 1991 request for this purpose?

Dr. Raub. The proposed January 1991 pay raise is estimated at $20.7 million, including the SES pay increase estimated at $3.2 million, and is included in the FY 1991 budget request.

PROGRAM EVALUATION EXPENDITURES

Mr. Early. How much does NIH normally spend of the one percent of appropriation that is available for program evaluation?

Dr. Raub. The table below reflects the level of support provided by the NIH over the past five years:

NATIONAL INSTITUTES OF HEALTH
(Dollars in Thousands)

	FY 1986	FY 1987	FY 1988	FY 1989	FY 1990
OS/ASPE	$ 5,694	$ 4,518	$ 4,794	$ 4,374	$ 4,746
OASH	2,845	2,641	2,501	2,296	2,059
NHANES	---	----	4,350	8,993	13,038
NMES	---	12,048	11,436	7,314	*
NCHSR/HCT	3,714	4,281	4,304	5,093	*
AHCPR	---	---	---	---	28,437
Subtotal	12,253	23,488	27,385	28,070	48,280
NIH PE	2,275	1,756	3,000	2,042	4,500
TOTAL	14,528	25,244	30,385	30,112	52,780

* Incorporated into the AHCPR

NHANES - National Health and Nutrition Survey
NMES - National Medical Expenditure Survey
NCHSR/ACT - National Center for Health Services Research and Health Care Technology Assessment
AHCPR - Agency for Health Care Policy Research

AHCPR

Mr. Early. Part of the funding for the new health care policy and research agency is to be derived from the one percent of appropriation NIH has available each year to conduct program evaluations. How much will be allocated for the AHCPR in FY 1990?

Dr. Raub. In FY 1990, the NIH is providing $28,354,000 in one percent funds to the Agency for Health Care Policy and Research.

Mr. Early. What is the estimate for 1991?

Dr. Raub. We don't know the cost for FY 1991 yet, but would expect that a similar level of support will be provided.

Mr. Early. Are these amounts, or decreases, reflected in the 1990 and 1991 columns of the budget justification? From where will these funds be taken--RPGs, Centers, Intramural? What impact will this have in FY 1990 and FY 1991?

Dr. Raub. Funds for the new Agency for Health Care Policy and Research (AHCPR) were not included in the 1990 or 1991 budget requests. We anticipate that the funds required for this new agency will be provided from a variety of budget mechanisms, but primarily from research project grants. There will be a slight decrease in the level of research support reflected in the FY 90 and 91 budget requests as a result of support for the AHCPR.

BIOMEDICAL RESEARCH TRAINING PROGRAMS

Mr. Early. NIH recently completed a review of its biomedical research training programs. Would you briefly summarize these recommendations.

Do you anticipate implementing any of these recommendations in FY 1991? If so, which ones, and could you give us an idea of the cost of implementing each?

Dr. Raub. The recommendations of the Task Force on Biomedical Research Training Programs focus on the improvement of three crucial elements of producing the biomedical research personnel of the future: means of recruiting and retaining the finest minds to biomedical research, the quality of the training, and achieving both of those goals at the least possible cost.

o The recommendations for recruitment and retention include:

- increases in stipends to levels approaching those of competing, parallel career options

  - modification of structure for National Research Service Award (NRSA) payback obligations
  - encouragement of early recruitment by allowing short term training of predoctoral students on training grants

- The recommendations for the quality of training include:
  - changes in review criteria of new and renewal applications for training grants
  - encourage training of M.D.s with Ph.D.s
  - require a minimal period of two years of research training for professional doctorates and flexibility regarding additional years of research training and career development
  - create databases and criteria for more detailed assessment of training programs so that the quality of programs can be monitored and improved in the future

- The recommendations for cost-containment include:
  - two-tiered cost of education allowance to replace full payment of tuition costs
  - increased efficiency of training programs by implementation of recommendations
  - create databases and criteria for more detailed assessment of training programs so that the efficiency of programs can be monitored and improved in the future

Implementation of these recommendations in FY 1990 and FY 1991 has begun with issues of program flexibility, training databases, and review criteria. There is no change in cost associated with the implementation of these recommendations.

Implementation of cost-related recommendations such as increased stipend levels and cost of education allowances are being considered for FY 1992.

STIPEND LEVELS

Mr. Early. Would you provide for the record a table displaying the stipend levels at NIH, at other Federal agencies, and House Staff salaries?

Dr. Raub. The following table provides the requested information.

Postdoctoral Years of Experience	National Research Service Award Stipends	1989-90 House Staff Salaries*	NIH Intramural Training Fellowships	Veterans Admin. Research Assoc.
0............	$17,000	$24,288		
1............	18,000	25,792		
2............	25,000	27,189	$25,000 to	
3............	26,250	28,537	35,000	
4............	27,500	29,861	28,000	COLA
5............	28,750	31,128		COLA
6............	30,000	---		
7 or more....	31,500	---		

*Estimate provided by Association of American Medical Colleges.

EXTRAMURAL CONSTRUCTION

Mr. Early. The FY 1990 bill included $15 million for extramural construction initiatives, to be used to address high priority programs. I understand that you have proceeded with the solicitation for proposals to address general construction needs as well as specialized programs for animals. Would you explain in greater detail what you plans are?

Dr. Raub. As a result of sequestration, the $15 million appropriated for construction grants has been reduced to $14.8 million. After an analysis of all of the applicable statutes, the language in the appropriations bill and the construction authorities in three of the institutes, NIH plans to allocate these funds as follows. Two Requests for Applications (RFAs) will be issued. One focuses on a single mouse breeding facility large enough to meet national and international resource needs. The second RFA is for all other construction projects falling within the NIH extramural construction authorities. In addition, because there are a number of applications already in house and reviewed with excellent priority scores, $2 million will be allocated to the NCI for these projects.

Because of the unique significance of the mouse breeding facility problem, it was determined that $10 million would be made available for this project. The awarding of these funds will be subject to peer review, and should the best proposal not be able to justify the full $10 million, NIH would make the award at the appropriate amount and make any residual funds available for the other competition. NIH's intent, however, is to be unequivocal in terms of the importance of the mouse breeding facility and to assure that an adequate sum is available to support it.

For the second RFA, the NIH focus will be in areas that fall within existing construction authorities. These areas include cancer; heart, lung and blood; and eye. Consistent with Congressional intent, NIH has taken a broad interpretation of these authorities and will make every effort to ensure that all possible candidates for funding will compete for it.

With regard to the $2 million allocated to the NCI for excellent projects that have already been reviewed, it is expected that awards will be negotiated with the top three facilities on the list. Should the entire $2 million not be required, the remaining amount would be made available for competition under the second RFA described above.

Mr. Early. I gather that you have "tapped" the various Institutes to develop a pool of these funds, and that the total NCI "tap" was $3.6 million. Is that correct? I also understand that you plan to return only $2 million to NCI to fund peer reviewed, approved proposals, and that NCI has numerous meritorious proposals awaiting funding. Are these plans to return more than the $2 million, or is that it?

Dr. Raub. After sequestration, NCI contributed $3.5 million to the total amount made available for construction. The $2.0 million that has been made available to NCI are for the top three grants that are currently approved and unfunded. Those NCI grants that remain approved and unfunded may compete for the remaining $2.8 million that has been set aside for the second RFA that focuses on projects that fall within the NIH construction authorities.

PROFESSIONAL JUDGEMENT BUDGET

Mr. Early. What was the NIH professional judgment budget for FY 1991, and how does it differ from the President's Budget request excluding AIDS?

Dr. Raub. Excluding AIDS, the professional judgment budget totals $9,530.2 million, an increase of $2,400.7 million over the President's budget of $7,129.5 million.

Mr. Early. Please provide for the record comparative tables displaying, by Institute and mechanism, the NIH professional judgment budget.

Dr. Raub. The following table provides the NIH Director's professional judgment budget at the aggregate NIH level. The individual Institute Directors provide their own professional judgment budgets when asked to do so by the Congress. We do not attempt to allocate the NIH Director's professional judgment budget by Institute.

BUDGET INCREASES

Mr. Early. If an increase over the FY 1991 request is provided for non-AIDS activities, how would you use these additional funds?

Dr. Raub. NIH's highest priority for use of funds above the FY 1991 request is the support of investigator-initiated research funded through research project grant awards. If additional funds were provided in the non-AIDS activities we would first increase support for this important mechanism. Funds would be added to increase the number of competing research project grants and to support the direct costs of competing and noncompeting grants at

NATIONAL INSTITUTES OF HEALTH

Professional Judgement Budget
(Dollars in Thousands)

(Excludes AIDS)

	FY 1990		FY 1991		FY 1991	
	Revised Appropriation		President's Budget		Professional Judgement Budget	
	No.	Amount	No.	Amount	No.	Amount
RESEARCH GRANTS						
1. Research Projects:						
Noncompeting......	15,188	3,008,579	14,731	3,075,714	14,731	3,388,507
Admin. Suppl......	(467)	22,707	(432)	21,037	(432)	21,037
Competing.........	4,394	877,067	4,856	1,011,946	8,269	1,817,626
Subtot.,RPG-New BA	19,582	3,908,353	19,587	4,108,697	23,000	5,227,170
2. Research Centers:						
Spec./Comp. Ctrs..	406	402,367	412	430,158	509	624,007
Gen.Clin.Res.Ctrs.	78	92,651	78	92,651	83	130,000
Biotech Res.Ctrs..	59	31,706	59	31,706	66	47,000
Lab An.Sc.&Pr.Res.	42	33,175	42	33,175	46	45,000
RCMI..............	17	15,965	20	20,595	20	22,000
Subtotal,Res. Ctr..	602	575,864	611	608,285	724	868,007
3. Other Research:						
Res. Career Prog..	1,522	103,688	1,528	104,137	2,000	145,600
Clinical Ed. Prog.	29	2,942	29	2,942	29	3,000
Coop. Clin. Res...	245	73,527	245	73,527	353	93,694
Bio.Res.Supp.Prog.	790	78,023	810	52,174	837	140,000
Min.Bio.Res.Sup...	98	39,432	98	42,785	98	48,493
Other Res. Rel....	1,153	67,555	1,161	68,317	1,546	108,261
Subtotal, Oth.Res.	3,837	365,167	3,871	343,882	4,863	539,048
Total, Res. Grants	24,021	4,849,384	24,069	5,060,864	28,587	6,634,225
4. TRAINING:						
Individual Awards...	1,872	48,609	1,916	49,659	2,136	59,879
Institutional Awards	9,618	230,736	9,799	234,461	10,564	278,124
Total, Training...	11,490	279,345	11,715	284,120	12,700	338,003
5. R & D Contracts......	1,060	377,858	1,064	384,915	1,655	570,000
6. Intramural Research..		733,489		780,021		940,000
7. Res. & Mgmt. Support.		291,526		311,952		335,000
8. Disease Control (NCI)		74,944		75,459		100,000
9. Construction.........		15,397		1,479		175,000
Subtotal, IRDs....		6,621,943		6,898,810		9,092,228
10. Nat'l Library of Med.		85,235		89,384		105,000
11. Off. of the Director						
OD................		32,896		35,791		37,017
AIDS..............		---		---		---
AREA..............		11,009		11,372		16,000
Dir.Discr.Fund.....		---		20,000		97,000
Supercomputer......		33,490		---		---
IR Radiology.......		1,970		2,065		2,065
Subtotal, OD.....		79,365		69,228		152,082
12. Buildings & Facil....		46,277		72,100		180,900
TOTAL...............		6,832,820		7,129,522		9,530,210

levels more consistent with study section recommendations and committed amounts. Other examples of program areas that would receive support are the following:

- Additional funds would be provided for research centers, other research and R&D contracts in order to maintain program balance and support these mechanisms at levels commensurate with the emphasis on research project grants.
- Research training would be increased in order to fund a greater number of research trainees and provide for a stipend increase.
- The research management and support mechanism would be increased in order to provide for the increased work load resulting from an expanded extramural program.
- Funds would be added for B&F for the following activities: construction of the Child Health/Neurosciences Facility and the Consolidated Office Building, NIEHS Facilities, asbestos removal, elimination of barriers to handicapped, renovations to radiation oncology space in Building 10, and repairs and improvements.
- Additional funds would be provided for the NIH minority programs.
- An increase would be provided to initiate several additional major new clinical trials.
- Funds would be added for the extramural construction authorities of the NCI, NHLBI, NEI, and the NIA, as well as for general extramural construction and construction for the Human Genome Program. These last two construction activities would require authorizing legislation.
- Funds would be added to expand the NIH intramural program.
- An increase would be provided to expand the Human Genome Program.

OPPORTUNISTIC INFECTIONS

Mr. Hoyer. Is there adequate funding for research on the opportunistic infections that can destroy the quality of life for individuals stricken with this disease?

Dr. Raub. The National Cooperative Drug Discovery Group (NCDDG) Program for Opportunistic Infections (OIs) is designed to address the need for more effective and selective anti infective agents. The NCDDG brings together scientists from academia, governments, and industry to facilitate the discovery and rapid development of new agents that are active against opportunistic pathogens. Patients with AIDS are highly susceptable to a wide-range of opportunistic infections. Given the diversity and number of pathogens, expansion of current efforts is needed to identify more effective and selective antiinfective agents.

AIDS BUDGET CHRONOLOGY

Mr. Hoyer. What was the NIH request, by Institute, for AIDS funding that went to the OASH, the Secretary and to OMB?

Dr. Raub. The following table outlines the funding request by ICD at each level.

DHHS-NATIONAL INSTITUTES OF HEALTH

CHRONOLOGICAL DEVELOPMENT OF FY 1991 AIDS BUDGET
(Dollars in thousands)

	NIH to PHS	PHS to DHHS	DHHS to OMB	President's Budget
NCI............	$208,141	$187,506	$167,059	$160,807
NHLBI..........	70,721	52,523	46,764	44,463
NIDR...........	10,504	6,987	4,740	5,002
NIDDK..........	29,866	10,069	6,089	5,791
NINDS..........	40,023	26,034	18,110	17,227
NIAID..........	580,457	497,629	445,417	423,407
NIGMS..........	20,736	19,505	16,414	15,487
NICHD..........	74,675	45,778	31,620	29,010
NEI............	8,414	7,814	6,284	5,887
NIEHS..........	4,815	4,823	4,823	4,580
NIA............	5,253	4,032	969	929
NIAMS..........	5,615	4,959	1,553	1,483
NIDCD..........	1,220	1,220	600	578
NCRR...........	103,290	52,413	49,350	48,379
NCNR...........	3,440	2,676	1,209	1,148
FIC............	8,501	7,008	5,409	5,207
NLM............	3,000	3,333	553	532
OD.............	14,238	14,271	12,726	13,747
B & F..........	85,500	49,200	16,500	16,500
Total..........	1,278,409	997,780	836,189	800,164

BRSG PROGRAM

Mr. Hoyer. Can you explain the changes that will result from the reorganization of the basic research support grant program, and the corresponding $17 million cut in that program for FY 1991?

Dr. Raub. In the FY 1991 Congressional Justification for the National Center for Research Resources (NCRR), $17.7 million is requested for the Biomedical Research Support Grant (BRSG) Program, a formula grant program activity currently designed to provide flexible funds to institutions that receive at least $200,000 in PHS research grant support. These funds are used by the institutions for various needs, best determined at the local level, including pilot research, bridging research support, and provision of central resources.

The FY 1990 budget proposes a change for this program targeting one-third of the funds ($5.9 million) to institutions to increase the participation of underrepresented minorities and the economically disadvantaged in biomedical research. The NCRR plans to utilize these funds by channeling them into the Minority High School Student Research Apprentice Program (MHSSRAP), a proven highly successful means of introducing minority high school students to biomedical research and fostering interest in careers related to health and research. A portion of the high school program funds (approximately 10 percent of the total budget of $8.5 million) will be set aside for a pilot program for high school science teachers, while the remainder will support 5,100 high school apprentices in 1991.

For the remainder of the funds in the BRSG formula program ($11.8 million), the current BRSG program will continue with the same eligibility requirements, in order not to exclude the large number of small institutions currently eligible, nor to affect the eligibility of these institutions for other NCRR and NIH programs for which the BRSG award is a requirement. In a major departure from previous program design, however, the size of the awards will be limited to a minimum of $5,000 and a maximum of $30,000. Awards will average $17,500.

RESEARCH PROJECT GRANTS

Mr. Hoyer. Between 1984 and 1987 the number of new and competing grants went from 5493 to 6447. At about the same time the average length of a research project went from a little over three to over 4 years by 1988. Some people are describing the "crunch" in new awards this year as an "out-year" problem that has caught up with us.

What percentage of approved projects competing for grants will be funded in fiscal years 1989, 1990, and 1991?

Dr. Raub. The award rate for fiscal year 1989 was 29.4 percent. Estimates for the award rates for fiscal years 1990 and 1991 are 24 and 25 percent, respectively.

Mr. Hoyer. How many new grants were funded in those same fiscal years?

Dr. Raub. In FY 1989, 5,382 new and competing grants were funded. Estimates for new and competing grants for fiscal years 1990 and 1991 are 4,633 and 5,095, respectively.

Mr. Hoyer. What percentage of approved grant applications should we fund?

Dr. Raub. We consider an award rate of 45 to 50 percent to be the level of grants funding that ensures support for essentially every strong project.

Mr. Hoyer. Have grant awards kept pace with the biomedical research and development inflation rate, and what are the recent year trends in the proportion of grant awards that are paid to institutions for indirect support of investigators?

Dr. Raub. The Biomedical Research and Development Price Index (BRDPI) projects increases of 5.7 percent in 1990 and 5.8 percent in 1991. We estimate our average cost increases for competing and noncompeting research project grants to be 5.9 percent in FY 1990 and 4.8 percent in FY 1991.

The following table shows the average indirect cost rate and the estimate of total expenses for these costs for the past 10 years.

NATIONAL INSTITUTES OF HEALTH
Indirect Cost Rates

	Dollars	Indirect Costs Awarded	Percentage
1981	$2,224,138	655,143	29.5
1982	2,300,534	689,855	30.0
1983	2,584,787	791,580	30.6
1984	2,958,266	921,627	31.2
1985	3,412,923	1,069,707	31.3
1986	3,564,061	1,119,115	31.4
1987	4,188,369	1,311,539	31.3
1988	4,540,758	1,416,716	31.2
1989	4,846,110	1,530,547	31.6
1990 Est.	5,080,114	1,625,636	32.0
1991 Est.	5,603,766	1,793,205	32.0

CHILD IMMUNIZATIONS

Mr. Hoyer. As you know, and as the justification indicates, the DPT inoculation can have mild or very serious side effects in children. How long will it take to complete trials of the new pertussis vaccine, and are there any examples of vaccines or drugs that are under development whose eventual testing and certification for use could or should be accelerated?

Dr. Raub. Work on the development of improved pertussis vaccines has accelerated rapidly during the last year. Over twelve different vaccines are presently under development and study. One of these, the NICHD pertussis toxoid vaccine is currently projected to begin Phase III large scale testing in Sweden in January 1991. This study will follow all 3,000 children enrolled until the age of 24 months, thus the earliest expected report of the efficacy of this vaccine will be in early 1994. Plans for a large scale trial of this vaccine in the U.S. are still in process.

The NIAID, as the prinicpal agency within the PHS for vaccine research and development, has initiated a Phase I/II clinical trial to determine the immunogenicity and general safety of all twelve of the candidate vaccines within its Vaccine Evaluation Units. A solicitation was recently issued by NIAID to try to identify sites where clinical trials to establish the efficacy of these vaccines can be conducted. This will be a long process and it is presently estimated that a clinical trial will require three to five years or perhaps even up to ten years, depending on the site selected and the trial design implemented.

The development of at least five other vaccines could be significantly accelerated. These include vaccines to prevent Group B streptococcal (GBS) infections in children, herpes virus, rotavirus infections, pneumococcal infections and hepatitis infections - Both hepatitis A and hepatitis C. All of these infections are responsible for significant morbidity and mortality, not only among our pediatric population, but also among adolescents and adults.

REPRODUCTIVE HEALTH

Mr. Hoyer. Dr. Raub do you have any data on the volume and level of support for research on reproductive health issues at NIH over the past ten years?

Dr. Raub. Within the National Institutes of Health, the focus for research on reproductive health is the National Institute of Child Health and Human Development (NICHD). Through its Center for Population Research, the NICHD supports a broad range of biomedical research in the reproductive sciences relevant to the problems of human fertility and infertility, the development of safe and effective methods for fertility regulation, the evaluation of the benefits and risks of current contraceptive methods, and demographic and behavioral sciences research on the causes and consequences of population structure and change.

The level of support for this activity over the past 10 years is provided below:

FY 1990 (Estimate)	$147,464,000
FY 1989	144,095,000
FY 1988	132,095,000
FY 1987	132,744,000
FY 1986	113,296,000
FY 1985	114,703,000
FY 1984	106,090,000

FY 1983	101,977,000
FY 1982	95,905,000
FY 1981	91,861,000
FY 1980	86,561,000

Mr. Hoyer. An Institute of Medicine committee estimates that 1.2 to 3 million unwanted pregnancies occur in the United States yearly. In the past twenty years, all major U.S. pharmaceutical companies except one have halted contraceptive research and development. To what extent is NIH able to respond to the opportunities in this area?

Dr. Raub. Since its creation in 1970, the Center for Population Research of the National Institute of Child Health and Human Development (NICHD) has funded a broad spectrum of projects with both the public and private sector including a number of pharmaceutical companies. Much of this research and development was designed to take up the slack resulting from the retreat of the U.S. pharmaceutical industry from this area which has continued over the past 20 years. The NICHD works with other government agencies, particularly the Agency for International Development, and with the drug industry in trying to have them take over products that the NICHD has developed and tested through the earlier phases of clinical trials. The Institute tries to encourage industry to pick up the costs and the efforts required for phase 3 clinical trials, and marketing, with mixed success. One of the remaining hurdles, however, is the problem of product liability insurance coverage for the testing of those products, both for us and for the pharmaceutical industry, and for those products once they are on the market.

FETAL TISSUE

Mr. Hoyer. Can you know how much in the way of private funds are devoted to fetal tissue research; how many grant proposals you received in this area of investigation most recently; how many were approved for funding, at what total dollar level?

Dr. Raub. Scientists receiving private support for their human fetal tissue research are under no obligation to share either their sources or levels of private funding. Consequently, the NIH does not know how much private funding is devoted to this area of research.

The reporting system in place for human fetal tissue research is not designed to provide specific figures regarding the total number of grant applications received that may have a bearing on this area of research. The system does report on the nature of the research project funded, and whether human fetal tissue is a major or minor component of the research effort. In FY 1989, NIH supported 85 projects involving the use of human fetal tissue in research in the amount of $7.3 million. The bulk of the research in this area, $6.6 million or 90 percent is conducted by extramural scientists.

WOMEN IN RESEARCH

Mr. Hoyer. Dr. Raub, can you tell the committee about the GAO study requested by members of the congressional caucus on women's issues regarding the routine exclusion of women and even female animals from much of medical research?

Dr. Raub. On January 22 of this year, staff of the General Accounting Office (GAO) met with Dr. Katherine L. Bick, Deputy Director for Extramural Research, NIH, to discuss this study and to determine the extent to which the NIH policy of inclusion of women in study populations of clinical trials has had the desired effect.

Dr. Bick pointed out that, since the NIH implemented the policy in 1987, determination at this early date of any effective changes is not yet possible. She provided GAO staff with names of NIH staff members who could assist the GAO in obtaining detailed statements on research protocols that look at gender differences. She also arranged for the Division of Financial Management, NIH, to provide a list of clinical trials that are underway and suggested that the GAO representatives might obtain information on intramural clinical trials through the Office of the Deputy Director for Intramural Research.

The GAO study team has since been in touch with various NIH staff members in order to examine specific files and to explore how best to obtain the requisite data. Staff of the Division of Research Grants has been assisting the GAO study team in locating appropriate applications. This study is still underway.

In its policies on this issue the NIH has not included language on female animals in research studies. The question of gender is not a factor in animal studies unless it is specifically required. To the best of our knowledge, the CAO is not including this particular issue in its current study.

Mr. Hoyer. How well is the 1987 NIH policy encouraging researchers to include women in clinical trials working?

Dr. Raub. The Office of Extramural Research has formulated procedures that remind program staff of these policies prior to their initiation of announcements of requests for applications, program announcements and requests for proposals for the conduct of clinical trials. These procedures insure that appropriate language appears in all such announcements. Several of the funding components are adding additional guidelines to their own procedures in this area. Sensitivity of the initial review groups also has been heightened on the issue.

As the GAO study progresses, the NIH also plans to monitor the outcome of the policy and will expect to make adjustments in its procedures as needed.

Mr. Hoyer. Has NIH ever refused to fund a study that did not comply with the policy, and under what circumstances are waivers permitted?

Dr. Raub. Since the implementation of the policy, the Office of the Director is unaware of any instances in which funding was refused because of noncompliance with the policy. The review groups rarely rate with fundable scores those applications whose protocols have serious defects, such as highly inappropriate selection of study populations. In other cases applicants have been willing to make appropriate adjustments in order to accommodate the work statements to the policy.

Granting of waivers would be appropriate when an applicant with an otherwise excellent study is able to demonstrate that recruitment of certain types of individuals to the study population is not possible, but only in such cases where the design of the study is not primarily dependent on the recruitment of that particular group.

Mr. Hoyer. What is your view on the need to include more women in the medical research supported by the NIH, and do you have any specific strategies that would help improve the current situation?

Dr. Raub. I am in complete accord with the recommendations of the Public Health Service Task Force on Women's Health Issues and with the current NIH policies that have been developed in order to carry out those recommendations. In implementing those policies I would stress the following:

- Continue to identify, as the Public Health Service Task Force on Women's Health Issues did in the past, those conditions and diseases unique to, or more prevalent in, women of all age groups. To this end the NIH Advisory Committee on Women's Health Issues is proceeding with such an agenda and will continue to make periodic reports and recommendations to the Office of the Director, NIH.
- As new women's health issues are identified (or as other such issues are found to not have been addressed adequately), the directors of the institutes should continue to formulate plans for initiating studies in these areas.
- Periodically remind the biomedical community of the continuing intent of the NIH to stress initiatives on women's health (by republishing the Guide announcement, for example), while, at the same time, maintaining a sensitivity on the issue among NIH extramural staff.

HEALTH AND BEHAVIOR

Mr. Hoyer. What percentage of funds does NIH plan to expend on research related to health and behavior in FY 1990 and FY 1991?

Dr. Raub. The NIH's past annual reports to the House and Senate Appropriations Committees have placed NIH's support for health and behavior research at about three percent of NIH's total research and research training budget. Recent discussions among NIH staff suggest, however, that frequent underestimations of funding levels have probably occurred in these past reports. Consequently, NIH staff have reviewed all awards made in FY 1989 with particular attention to possible sources of error. As expected, this more accurate estimation of NIH's funding of health and behavior research places the total at $258 million or about 4.3 percent of the NIH budget for extramural and intramural research and research training in FY 1989. While overall NIH expenditures in FY 1990 and FY 1991 will be at this same level, the NIH has initiated a process to develop an NIH-wide plan for increasing its support for health and behavior research over the next ten years.

Mr. Hoye. Dr. Raub, what specifically has the NIH done in response to the report language accompanying last years appropriation bill regarding the need for NIH to increase the percentage of its funds expended on health and behavior research?

Dr. Raub. Like the Committee, the NIH recognizes the contributions of behavioral factors to health and the need to assure adequate levels of support for research in this area. Towards this end, the NIH has taken steps to assess the current status of NIH-supported research on health and behavior and to consider future research directions and opportunities. The NIH submitted its report to the Senate Appropriations Committee at the end of February 1990. The report provides examples of future research directions such as behavioral epidemiology of stroke or sensory disorders; health-related behaviors affecting low-birth-weight infants or HIV-positive patients; basic biobehavioral mechanisms of obesity or arthritis; and behavioral interventions to prevent injuries or to improve the health or minorities. Moreover, this report puts into place a continuing process for an orderly development of a long-range plan.

The NIH views health-related behavioral research as an integral part of its research and training programs. Each NIH Institute will assess the potential contributions of health and behavior research to fulfilling its mandate, contingent upon the scientific quality of research applications received. In order to identify more fullv this potential and to foster high quality applications, the NIH Working Group on Health and Behavior will coordinate an NIH-side planning effort and deliver a set of recommendations to the Director, NIH, and the Institute Directors by September 30, 1990. These recommendations will include methods for improving the financial tracking of health and behavior research supported by NIH; identification of appropriate and promising research initiatives within each Institute; and plans for increasing the level of support for health behavior research over a ten-year period. These recommendations, as discussed and approved by all NIH components, will then provide the report and long-term plan requested by the Senate.

HUMAN GENOME INFORMATION

Mr. Dwyer. Public Law 100-607 established a National Center for Biotechnology Information (NCBI) at the National Institutes of Health (NIH) within the National Library of Medicine. NCBI's responsibilities include integrating existing data bases, developing new computer analysis programs, and improving data access.

Dr. Watson has stated that the 15-year project to map the human genome will officially begin October 1, 1990. Will NCBI be working to assist the National Center for Human Genome Research and the Department of Energy's human genome project in disseminating their discoveries? Do you believe that your fiscal year 1991 budget request will be adequate?

Dr. Raub. The National Center for Biotechnology Information will work with both the National Center for Human Genome Research (NCHGR) and the Department of Energy in order to disseminate information developed within the human genome project. For the past year, the NCBI has collaborated with the NCHGR in planning a coordinated informatics approach to deal with the scientific data as it moves from the laboratory to the public. Laboratory data management is an area that will be funded by the NIH Center for Human Genome Research. The NCBI will assist as necessary in the design of database systems for laboratory informatics, with special emphasis on issues regarding the transfer of laboratory data to public access databases. The NCBI considers it crucial to build sound data management architectures to cope with the volume and complexity of the data and therefore a high priority has been given to the design of database systems that can accommodate input from a variety of sources and interconnect with other specialized databases to reduce duplication of effort. The NCBI is also cooperating with the DOE and participants in the Joint Information Task Force (which coordinates NIH/DOE genome efforts). At the working level, the NCBI maintains contacts with the database groups at Los Alamos National Laboratory and Lawrence Berkeley.

We believe that the FY 1991 budget request will be adequate to cover the expected data rates over the next year as well as support for research and development of new database systems. We expect that some increase in funding for follow-on years will be necessary to keep pace with the volume of data and the anticipated increase in size of the user community needing access to the data.

NCBI COMPUTER SUPPORT

Mr. Dwyer. Does NCBI have a supercomputer? What hardware and software investments will NCBI need as the human genome project begins its work?

Dr. Raub. The NCBI has high-speed network access to the NIH Cray X-MP at the Frederick Cancer Research Facility and to the IBM 3090 and its vector processing facility at the Division of Computer Research and Technology on the NIH campus. These machine resources have proven useful for the few specialized computing applications which take advantage of the architecture. The IBM 3090 has also been useful for a number of jobs with unusually large memory requirements. Many of the data retrieval and analysis programs, however, do not lend themselves to vector processing, therefore, the NCBI has concentrated on building a network of high-performance computer servers based upon scaleable processors which permits relatively low-cost CPUs to be used in multi-processor configurations or distributed across the network. This approach permits taking advantage of the rapid advances in processor speed by upgrading or incrementally adding new processors to the system. Since the systems used for code development at the NCBI share a common operating system and hardware base that are likely to be found in academic and industrial laboratories, NCBI software and database systems will be readily useable in those environments.

NCBI carefully assess hardware and software technology to insure that it can make effective use of the advances internally and for projects that will be disseminated to the biology research community. The FY 1991 budget is adequate for supporting intramural computer research and for the initial stages of public access to the databases the NCBI will support. Some increases in funding to provide additional high-speed storage and multi-processor data access machines would be anticipated in the follow-on years as the user community grows. It should be noted that our public access plans are based on the increasing availability, use, and performance of Internet, the NSF-supported National Research Network.

NCBI SERVICE ACCESS

Mr. Dwyer. How does an individual researcher or an institution utilize NCBI services? How will foreign researchers utilize NCBI's services? Will there be any fees, etc. assessed to the inquiring researcher for data retrieval or any other service?

Dr. Raub. For the last two years, we have offered access to fifteen sequence and factual molecular biology databases to researchers on the NIH campus through the IRX retrieval system. This same software, developed at the NLM, has been made available to Johns Hopkins School of Medicine to provide access to Dr. Victor McKusick's online Mendelian Inheritance in Man (OMIM) database and to GenBank for its online service.

Within the past year the NCBI has developed state-of-the-art algorithms for sequence similarity searching, multiple sequence alignment, and correlation of restriction and genetic maps. These programs are made available upon request to researchers.

Currently underway is the building of an integrated DNA and protein sequence database (GenInfo Backbone Database) which contains sequence information from the journal literature. This database will be distributed in a format conforming to an ISO data description standard (ASN.1) and in relational tables on CD-ROM and magnetic tape. The data will also be made available for network downloading via the Internet.

Finally, in FY 1991 the NCBI will provide online access to the GenInfo Backbone Database and to high-speed search software via the

Internet. The goal is to provide sophisticated retrieval and analysis tools for sequence and bibliographic data.

Foreign researchers are currently able to request software and, if connected to the Internet, will be able to access the online services. At this time, the only fees being assessed are for cost and recovery of the distribution media, e.g., diskettes, magnetic tape.

Mr. Dwyer. What other countries utilize NCBI services? Do any other countries have comparable facilities? If yes, does NCBI maintain ongoing working relationships with these facilities?

Dr. Raub. NCBI has a working relationship with the DNA database developers at the European Molecular Biology Laboratory (EMBL), Heidelberg, Germany and is in contact with the Human Genome Organization (HUGO), whose U.S. office is on the NIH campus. Of the known organizations in other countries, only the MBL has some degree of similarity with the functions of the NCBI. The NCBI is unique, however, in the size and experience of its intramural research group working in the area of computational molecular biology and in its mandate to coordinate public molecular biology data. Its location on the NIH campus gives it ready access to thousands of biomedical researchers. The NCBI is also distinguished by being part of the world's largest medical library and is therefore in contact with an established user community of biomedical information services.

Mr. Dwyer. In recent weeks, much controversy has been generated over the underutilization of women in clinical trials and other studies. The most publicized case was the aspirin/heart attack study. What efforts will the various Institutes make to include women, and also minorities, in future studies?

Dr. Raub. All of the extramural funding components of the National Institutes of Health (NIH) have agreed to the policies first published in the NIH Guide for Grants and Contracts on January 23, 1987 (for women), and on September 25, 1987 (for minorities). These policy statements affirmed the recommendations of the Secretary's Task Force on Black and Minority Health in its October 1985 report and those of the Public Health Services Task Force on Women's Health Issues in its January 1985 report. The Guide announcements alerted the biomedical community of the intent of the NIH to ensure that minority and women populations will be included in the populations of clinical research studies. Special emphasis is placed on studies of diseases that disproportionately affect minorities and on conditions and diseases unique to, or more prevalent in, women of all age groups. This applies to studies carried out under the grant, cooperative agreement and contract instruments.

The funding components also agreed to abide by the internal NIH I&I Memorandum OER 89-3, published on July 1, 1989, which requires that all announcements of requested research studies (Requests for Applications, Program Announcements and Requests for Proposals) carry language appropriate to this policy, alerting applicants and offerors that inclusion of women/minorities in the study populations of their proposed study is a requisite part of the application/proposal.

The I&I Memorandum also alerted executive secretaries of the initial review groups of the institutes and of the study sections in the Division of Research Grants of the requirement to brief review group members on this policy and to ensure that the members address specifically whether the procedures outlined in the application conform to the policy. Executive Secretaries then must summarize in the Summary Statement the findings and recommendations of the reviewers on this issue.

Several of the funding components have developed specific guidelines and procedures for insuring adherence to these NIH-wide policies.

CHRONIC DISEASES

Mr. Pursell. As a member of this subcommittee, I have been an adamant supporter of NIH, and I was very pleased with the large increase NIH received in FY 1990. I am optimistic that we can provide funding above the President's request for FY 1991.

When Secretary Sullivan was before this subcommittee last month, I shared my concern regarding chronic diseases with him. Approximately 70 percent of all premature deaths and disabilities in the United States are caused by six chronic diseases (cancer, heart disease, stroke, diabetes, hypertension) and smoking. Michigan has the highest death rate from chronic diseases.

While the death rate for cardiovascular disease, for example, has declined in the past decade or so, do you believe enough is being done to fully utilize the information that NIH has available through its research?

Dr. Raub. The NIH commitment to health promotion, health information, and particularly disease prevention continues to grow. The following examples reflect the NIH commitment and demonstrates the multiplicity of programs directed at helping the American public adopt a healthier lifestyle.

National High Blood Pressure Education Program (NHLBI)
National Cholesterol Education Program (NHLBI)
National Blood Resource Education Program (NHLBI)
Public Education on Arthritis, Musculoskeletal and Skin Diseases (NIAMS)
Public Information for the Elderly through the "Age Page" (NIA)
Smoking Cessation Information Programs (NCI, NHLBI, NICHD)
Breast Cancer Education Program (NCI)
Cancer Prevention-Awareness Program (NCI)
Intervention Strategies to Prevent Teenage Pregnancy (NICHD)
Oral Health Education (NIDR)
National Clearinghouse for Diabetes, Digestive Disease, and Kidney and Urologic Diseases (NIDDK)
Water Safety and Health Training (NIEHS)
Asthma Self-Management Education (NHLBI)

This listing is representative only, and is far from inclusive of the many NIH health promotion and education programs.

PREMATURE DEATHS

Mr. Pursell. Is the federal government spending enough to help prevent premature deaths?

Dr. Raub. There are many avenues for additional research regarding prevention of premature deaths that could be pursued by the NIH. On the basis of testimony supplied by expert witness' at recent PHS sponsored regional meetings, there is a dire need for additional service-oriented support toward preventing premature deaths.

Mr. Pursell. To what extent do you work with CDC in this regard?

Dr. Raub. The NIH and CDC were joint participants in recently sponsored PHS regional meetings, and collaborative efforts in all aspects of disease prevention continue through regularly scheduled and sponsored meetings and conferences. NIH and CDC are regularly represented in PHS efforts directed at the 1990 and Year 2000 Health Objectives. In addition, NIH and CDC, as well as other PHS agencies, are collaborating toward developing a PHS Plan to Strengthen Public Health in the U.S.

In addition to the above, NIH and CDC are engaged in many more joint efforts involving every aspect of disease prevention and health promotion.

NIH SUPPORTED RESEARCH

Mr. Pursell. In recent months, I have been contacted more and more by researchers, in my district and in other districts, regarding the percentage of NIH grant applications being funded. Although I am sure the percentage varies by the particular Institute, most seem to agree that funding is now made available to approximately the top 12-15 percentile, as opposed to the top 20-30 percentile several years ago.

I realize that one reason for this is because new grants are being funded for five years, rather than three years as was the case. However, in light of the record level of funding for NIH, do you believe the research community, the medical community, and the taxpayer are getting the most for their dollar?

Dr. Raub. The National Institutes of Health continuously examines various cost-benefits aspects of NIH-supported research. One part of such an effort has focused on identifying the cost implications of the investment of NIH applied research and clinical trial funds used to confirm the appropriateness of new health care advances or changes in health care delivery. Twenty-six examples have been identified and studied over the last several years.

The examples involve several different health care areas. These include diagnosis/screening, new therapies, prevention, and evaluation of existing practices. In a few instances, combined areas are involved. In several cases, the impact of the health care advance concentrates mostly on children or youth, while a number involve primarily adults. All age groups are involved in a few instances. Overall, results from this analysis indicate that investments in biomedical research result in significant health benefits to a broad base of the U.S. population. At the same time, however, it is clear that additional efforts are needed in some areas to ensure future progress in the transfer of emerging as well as already developed technologies. For example, we are embarking on an era during which basic information about the genetic modification of cellular function as well as information about the human genome will become available from NIH-sponsored research. Continued emphasis on translating this information into potential therapies for a wide range of diseases is imperative. At the same time, it is also important that NIH continue to transfer information obtained from sound biomedical research to recommendations concerning life-style changes that can enhance disease prevention.

The following table provides a useful summary and overview of the results of the analysis. In order to summarize the results over a number of years, all calculations have been converted to 1989 prices. The total NIH investment in applied research and clinical trials across all the examples and years amounts to approximately $800 million in 1989 prices. The comparable realizable one-year savings (again expressed in 1989 prices) range from a low of about $5.2 billion to a high of nearly $6.7 billion, depending on the conservatism of the set of assumptions chosen. The lower figure suggests an annual rate of potential return of $6.50 for a dollar invested; the higher figure carries an even more impressive $8.80 for the same dollar.

Some specific examples are summarized below. In these cases, the investment and savings figures are expressed in the prices of the year in which the example was developed.

- Saving close to 900 newborns annually from a lifetime of arrested physical and mental development through development of a mass screening device for neonatal hypothyroidism. The total NIH costs for targeted applied research and clinical trials has been estimated at about $1.2 million with a potential one-year savings of over $206 million;

- Development of laser-based photocoagulation treatment for early stage diabetic retinopathy. This can arrest what would become a chronic and crippling disease at a later stage and has resulted in potential one-year savings of over $2 billion. The total NIH investment for a clinical trial was $48.2 million;

- During the last decade NIH-supported research has identified the metabolic abnormalities which underlie the formation of kidney stones. This, in turn, has led to the development of a relatively simple and inexpensive potassium citrate treatment for the prevention of the recurrence of kidney stones among the estimated 198,000 patients susceptible to such a condition. Slightly over $679,000 was expended for research grants to pay for the research effort. It is estimated that close to $300 million in annual treatment costs and lost work days can be saved from this advance;

- Validation of the advantages of outpatient breast biopsies has made possible a two-stage breast cancer procedure that provides an alternative for more than 490,000 women annually who would otherwise suffer the anguish and uncertainty of combined diagnosis and treatment under general anesthesia. A total of $10.6 million of the NCI National Surgical Adjuvant Breast Project was expended from 1971 to 1986 to perfect this procedure. Potential one-year reduced diagnosis and treatment costs are estimated at upwards of $169 million.

- Development of cisplatin in combination therapy for treatment of advanced stage testicular cancer has provided new hope for victims of this disease. Testicular cancer is the most common malignancy in 15-35 year old males and is the most frequent cause of cancer-related deaths in this age group. The new treatment not only significantly increases the survival rate but reduces work days lost by premature mortality and morbidity. This translates into a potential one-year saving for the nation of upwards of $109 million. NIH funds invested in the discovery and development of cisplatin over a 17 year period amounted to less than $56 million.

- An improved vaccine for the prevention of Haemophilus influenza type b (Hib) disease in the 18 month to 5 year age group has been developed with NIH funds. Hib is a leading cause of bacterial meningitis in the United States. Prevention of meningitis also protects a number of surviving children from a variety of neurological sequelae, including hearing loss, vision impairment, mental retardation and seizure disorders. The estimated net cost savings realizable from the reduction in premature mortality and elimination of long-term earning losses are close to $146 million annually. Total NIH research support during a 17 year period was $15.6 million.

- An assay for detection of HIV antibodies in the sera of individuals exposed to the HIV virus which can save 891 transfusion recipients from HIV infection annually has been developed with NIH funds. This translates into a potential one-year savings of slightly over $63.7 million. Total NIH expenditures for the development and evaluation of the blood test from 1984-1989 was $6.7 million.

- Development of adjuvant therapy with levamisole and 5-fluorouracil (5-FU) for Dukes' C Colon Cancer. This new treatment significantly delays tumor recurrence and reduces patient risk of dying of recurrent colon cancer by one-third. Over 22,000 patients are diagnosed with this condition annually. Potential cost savings resulting from reduction of premature mortality and lost work days add up to close to $136 million annually. Total NIH investment since 1978 has amounted to $10.8 million.

- Development of a combined cytotoxic drug and steroid treatment for patients suffering nephritis resulting from systemic lupus erythematosus has been found to support life-supporting renal functions beyond five years at a considerably greater rate than earlier interventions. This provides hope for the more than 1,000 nephritis victims who each year are afflicted with this disorder. The realizable annual cost savings associated with this advance are estimated at close to $70 million. The NIH support totaled $9.8 million since 1970.

The remaining examples involve advances in diagnosis, improved therapy, vaccine or chemotherapeutic agent, and confirmation of ineffectual or inappropriate current practice. Realizable annual cost savings for these examples range from 2.6 to 258 million dollars.

POTENTIAL ANNUAL HEALTH CARE COSTS SAVINGS RESULTING FROM NIH INVESTMENTS IN APPLIED RESEARCH ANC CLINICAL TRIALS, BY YEAR OF EXAMPLE AND ICD

(Dollars in Millions)

Year	ICD	Total Support (1)	Low Realiz. Savings (2)	High Realiz. Savings (2)
1986	NHLBI	32.8	296.6	593.1
1986	NHLBI	6.7	12.2	107.0
1986	NHLBI	0.5	2.1	3.0
1986	CC	0.4	15.4	30.7
1986	CC	0.0	1.1	2.3
1986	NIAID	28.5	54.4	108.9
1986	NIAID	2.2	6.2	6.2
1986	NIAID	4.0	20.8	41.6
1986	NINDS	10.9	15.9	15.9
1986	NCI	12.9	194.1	388.4
1986	NEI	58.5	1,643.7	2,643.7
1986	NICHD	1.5	237.0	237.0
1986	NIDDK	0.8	344.6	689.3
		159.6	3,844.0	4,867.0

Year	ICD	Total Support (1)	Low Realiz. Savings (2)	High Realiz. Savings (2)
1988	NINDS	2.2	54.8	73.1
1988	NICHD	8.9	227.7	303.7
1988	NIAID	9.2	57.6	76.8
1988	NIAID	17.3	119.4	159.2
1988	NHLBI	0.3	11.6	15.5
1988	NCI	61.6	119.7	169.6
1988	NCI	19.1	96.0	128.0
		118.6	686.8	915.7

Year	ICD	Total Support (1)	Low Realiz. Savings (2)	High Realiz. Savings (2)
1989	NIDDK	492.3	537.3	476.3
1989	NIAMS	10.3	73.1	97.5
1989	NCI	7.0	50.1	66.7
1989	NCI	11.4	142.4	189.9
1989	CC	0.4	28.3	37.7
1989	CC	0.4	32.0	42.7
		521.8	683.2	910.9
TOTAL ALL YEARS		800.0	5,214.0	6,693.7

(1) 1989 values calculated using BRDPI Index Values, 1989 = 100
(2) 1989 values calculated using CPI Index Values, 1989 = 100

RESEARCH PROJECT GRANTS

Mr. Pursell. Have indirect or overhead costs had any effect on the decrease in the number of applications funded?

Dr. Raub. Since the individual rate has stabilized and remained at about 31 to 32 percent of total cost for the past several years, I don't believe indirect cost is a significant factor in the decrease in the number of grants currently being funded as it had been in earlier years.

Mr. Pursell. What percentile does NIH consider ideal?

Dr. Raub. We do not consider percentile paylines to be the best measure of our capacity to fund research. We consider the award rate to be a more relevant indicator and 45 to 50 percent to be the level at which essentially all strong projects are supported.

OFFICE OF SCIENTIFIC INTEGRITY

Mr. Porter. Last year I asked your predecessor Dr. Wyngaarden about research fraud within the scientific community. I understand that the Department has taken several steps to eliminate and to police fraud at NIH.

NIH now has an Office of Scientific Integrity which is charged with investigatory responsibilities. How long has this office been up and running?

Dr. Raub. The creation of the Office of Scientific Integrity (OSI) was announced in March 1989. The Office has been functional since April 1989. The OSI is responsible for handling misconduct situations for the entire Public Health Service, including the NIH.

Mr. Porter. There is also an Office of Scientific Integrity Review which is located in the Office of the Assistant Secretary. As I understand it, the Review panel is charged with adjudication. Has NIH sent any investigations to the Review panel for adjudication?

Dr. Raub. The OSIR, among other responsibilities, reviews reports of investigations that have been completed by the OSI or completed by an institution, with oversight by the OSI. There is no "Review Panel" as such; neither is the OSIR responsible for "adjudication," in the usual sense of the word. Rather, the OSIR reviews the investigation reports for thoroughness and objectivity, and forwards the reports, together with recommendations originated by the OSI, to the Assistant Secretary for Health.

Mr. Porter. At what point does NIH's Office of Scientific Integrity become involved in an allegation of fraud?

Dr. Raub. The OSI may be involved in situations of possible misconduct at the very outset, i.e. when an allegation is made directly to the office. At the other extreme, the office may become involved only after an inquiry has been done by an applicant/awardee institution, and a decision made that a formal investigation is warranted.

Mr. Porter. When does OASH become involved?

Dr. Raub. The OSIR (OASH) generally becomes involved in misconduct cases after a formal investigation has been completed.

Mr. Porter. Is there good coordination between these two bodies?

Dr. Raub. Coordination between the offices is excellent.

Mr. Porter. Is NIH adequately staffed to handle the 72 cases currently pending before OSI?

Dr. Raub. The OSI is slated for 16 full-time positions for FY 1990. We believe this is adequate staff to handle the caseload.

FEDERAL TECHNOLOGY TRANSFER

Mr. Porter. Passage of the Federal Technology Transfer Act (FTTA) of 1986 significantly changed the relationship between NIH and industry. Scientists at NIH are now encouraged to collaborate with private industry, and through Cooperative Research and Development Agreements (CRADAs) may receive a share of royalties generated by commercial exploitation of cooperatively developed products. These changes are designed to direct scientific advances to the marketplace more efficiently.

Would you tell me generally your impressions of this legislation, is it working well?

Dr. Raub. It is our view that the Federal Technology Transfer Act provides significant incentives for collaborative research and development efforts between NIH and industry scientists. The NIH has established an active implementation program, consisting of a Patent Policy Board, supported by a number of working subcommittees, as well as a new Office of Technology Transfer (OTT) which provides the organizational focal point for FTTA implementation. A network of Technology Development Coordinators within the Institutes, Centers, and Divisions of NIH participate with the expert staff of the OTT to assure timely and effective administration of the Technology Transfer Program. As of March 1990 about 130 cooperative research and development agreements have been approved, over one-fourth of which are with small businesses.

Mr. Porter. What is the potential for conflicts of interest under the FTTA?

Dr. Raub. As in many of the other endeavors undertaken by government employees, the potential for conflict of interest exists in collaborations with industry. A variety of situations could arise in which an NIH scientist might engage in activities which are not in the best interest of the government or the public. For example, the possibility for potential financial gain through patent royalties could cause an NIH scientist to refocus his or her research activities in areas that are not appropriate to the NIH mission. On the other hand, the legislation is meant to spur the development of technologies in the public interest. The ability of NIH scientists to consult for companies on outside work provides a form of interaction which is quite different from the official duty collaboration under a CRADA. Recognizing the inherent problems created by this disparity, the Director, NIH, convened a retreat on Conflict of Interest in Collaborations with Industry, in December 1988. Following the retreat and discussions of these problems in various committees, a draft Manual Chapter on Conflict of Interest in Collaborations with Industry is being drafted within the Office of Intramural Research, NIH.

Mr. Porter. How does NIH oversee these potential conflicts?

Dr. Raub. It is the responsibility of the individual scientist, of the scientific leadership staff of the NIH intramural program, and of several NIH offices to avoid real or apparent conflicts of interest or to identify and correct any conflicts that may occur. The Manual Chapter mentioned above will document the policies and procedures to be followed. The responsible officials include the hierarchical administrative leadership in the intramural program ranging from the laboratory or branch chief, the scientific director, as well as the technology development coordinators and director of each Institute/Center/Division (ICD). Each proposed CRADA is reviewed initially by the Office of General Counsel and the Director, Office of Technology Transfer, after which it is considered by the full CRADA subcommittee, which may refer potential conflict of interest situations back to the ICD Ethics Counselor. Each principal investigator on a CRADA is asked to complete a Conflict of Interest and Equal Access form. In situations where a scientist has previously engaged in consultation or lecturing for a company, coordination is also carried out with the Ethics Officer, Labor Management Branch of the Division of Personnel Management, which implements the outside work and activities approval system.

Mr. Porter. Under the FTTA, an NIH inventor may receive up to $100,000 annually in royalties from his contributions to drug development. Are there any circumstances under which he can receive more than $100,000 annually?

Dr. Raub. According to the royalty-sharing formula adopted by the NIH, the inventor(s) receive 25 percent of the first $50,000 (of license fee and royalty income), 20 percent of the second $50,000, and 15 percent of amounts over $100,000, based on cumulative income. On very large amounts of royalty income, therefore, the calculated inventor share could, each year, greatly exceed $100,000. However, the FTTA limits each government inventor to a maximum of $100,000 annually.

Mr. Porter. Does the President have the authority to waive that limit?

Dr. Raub. Yes, the FTTA authorizes the President to waive the annual limit. The President might wish to waive the $100,000 annual limit in exceptional cases to furnish an added reward or incentive for a particularly valuable or noteworthy contribution. An example might be a cure for AIDS or for cancer. A contributory rationale would be that for many university inventors, their share in royalties on inventions made under government grant support (as authorized by P.L. 96-517 [The Bayh-Dole Act]), is not subject to any annual maximum amount.

Mr. Porter. If so, are any NIH scientists receiving more than $100,000 annually? How many?

Dr. Raub. There are no NIH scientists currently receiving more than $100,000 annually. However, the Royalty Subcommittee of the Patent Policy Board will be considering the desirability of drafting guidelines to request such a waiver.

Mr. Porter. Non-inventor contributors may also receive product royalties. What are the limits for non-inventors? May they receive cash, or only in-kind contributions?

Dr. Raub. At the NIH, the awards to non-inventor contributors are made annually on a case-by-case basis by the ICD Director with the advice of the Scientific Director. No more than one-half of what is received by inventors would be paid to non-inventors. If non-inventor awards are made, it would be anticipated to be in cash, rather than in-kind.

Mr. Porter. Given that NIH researchers may now benefit from commercial exploitation of their inventions, the FDA approval process is of critical importance to the financial well-being of NIH personnel. Particularly at a time when NIH scientists are drastically underpaid, I can envision situations in which NIH might exert pressure on FDA to accelerate approval of NIH-developed products. Is there any basis for this contention?

Dr. Raub. The NIH believes that, while such a situation conceivably could occur, if an NIH inventor inappropriately tried to influence the FDA, the possibility should be further minimized by issuance of the Manual Chapter on Conflict of Interest in Collaborations With Industry. Efforts will be made in our semi-annual technology transfer training sessions for NIH scientists and administrators to sensitize them to avoid such inappropriate behavior and to inform them of the reasons for scrupulously avoiding actions that could be construed as inappropriate efforts to influence FDA regulatory decisions.

Mr. Porter. What is the relationship between NIH and FDA?

Dr. Raub. The NIH and the FDA are sister agencies within the Public Health Service and under the supervision of the Assistant Secretary for Health. The NIH supports and conducts basic and clinical biomedical research whereas the FDA is a regulatory agency for assuring the efficacy and safety of drugs, food additives, and medical devices.

Mr. Porter. How has this relationship changed as a result of FTTA?

Dr. Raub. There has been no intrinsic change as a result of the passage of the Federal Technology Transfer Act. The FTTA applies essentially to research scientists and therefore would not be applicable to those FDA scientists engaged only in regulatory work. FDA officials are invited to attend meetings of the NIH Patent Policy Board in a liaison capacity.

Mr. Porter. I received a letter in December from Reid Adler who is the Director of the Office of Invention Development (OID). Mr. Adler told me that OID is conducting a review of NCI's role in the development of AZT. When will that review be completed? Will you share the results of that review with my office?

Dr. Raub. Mr. Adler, Director of the Office of Technology Transfer (formerly called the Office of Invention Development) is spearheading a review of the development of AZT. A critical step involves a legal analysis being sought from the Patent Branch, Office of the General Counsel. It is anticipated that the review should be available by the end of April. It's further disposition will have to be taken under advisement by the appropriate offices within the Public Health Service and the Department of Health and Human Services.

FETAL TISSUE

Mr. Porter. The scientific use of human fetal tissue has generated a great deal of controversy in the past two years. What is the Department's current policy on the use of human fetal tissue? Is this policy being reviewed?

Dr. Raub. Human fetal tissue continues to be used in Federally sponsored biomedical research. In fact, human fetal tissue has certain unique characteristics that make it invaluable in biomedical research. These general properties make fetal cells useful in establishing cultured cell lines to study the response of organisms to hormones, drugs, and other environmental influences. The only restriction involving the use of fetal tissue from induced abortions applies to its use in transplantation research with human beings. This moratorium was declared initially in a March 22, 1988 memorandum from the Assistant Secretary for Health, and was sustained indefinitely on November 2, 1989, by the Secretary/DHHS in a letter to the Acting Director of NIH. The current policy of the Department as stated in Secretary Sullivan's letter is:

- "that there is no statutory mandate requiring Departmental support of such research."
- "the only legislation specific to this issue is found in Section 498 of the PHS Act which has as its focus the prohibition of certain kinds of live fetal research. Certainly nothing in that legislation or its legislative history requires the Department to fund fetal research."
- "The Department has been no more successful than the Congress in developing consensus on this issue. It has been studied and restudied. Most recently we have had a 'Report of the Human Fetal Tissue Transplantation Research Panel,' and a 'Report of the Advisory Committee to the Director, National Institutes of Health.' Despite all of this review and analysis, the debate on this issue continues to be intense and often bitter. In addition, I am aware that the legal debate surrounding the recently decided Supreme Court decision of Webster v. Reproductive Health Services has raised anew issues implicating the rights of fetuses, leaving unsettled just where the balance in this complicated mix of rights will eventually rest."
- "...I conclude that I should continue the moratorium of March 22, 1988, indefinitely. In taking this action, I am cognizant not only of the extensive review undertaken by the Panel [Human Fetal Tissue Transplantation Research Panel] and the Committee [Advisory Committee to the Director, NIH], but also of the extensive opportunity provided to the public to express its opinion and enter into this decisionmaking process."

Mr. Porter. Last year, Dr. Wyngaarden listed research on Parkinson's Disease as one of the most important advances at NIH during 1988 and 1989. This research consisted of implantation of non-human neural fetal tissue into monkeys with Parkinson's syndrome. However, your budget justification for FY 1991 makes no mention of this technique. What is the status of the neural fetal tissue implantation research?

Dr. Raub. NIH grantees, specifically those supported through the National Institute of Neurological Disorders and Stroke (NINDS), are engaged in a number of research efforts that study the feasibility of pre-term placental tissue for the stimulation of dopaminergic fiber regeneration in monkeys with MPTP induced Parkinsonian symptoms. Other work involves a search for growth factors using in-vitro neural cell growth. Yet other research efforts in this area involve exploring approaches using implantation of biological materials other than fetal tissue, such as genetically modified skin cells (fibroblasts) to secrete nerve growth factor. This is an important area of research in that these biological materials exhibit some of the characteristics that make fetal tissue suitable for implantation, such as the ability to stimulate proliferation and/or cellular activity in the transplant recipient. For example, in recent animal studies, scientists had successfully transplanted genetically engineered fibroblasts into the brains of rats with a syndrome resembling Parkinson's disease. Engineered to secrete the brain chemical dopamine, which has been found in short supply in Parkinson's patients, the cells greatly reduced the rats' symptoms and even demonstrated enhanced sprouting of the axon portion of nerve cells. Estimated funding for this type of research in FY 1990 is $1.48 million.

Mr. Porter. Has the Department's policy on the use of human fetal tissue inhibited promising research on Parkinson's Disease?

Dr. Raub. While the moratorium on the use of human fetal tissue derived from induced abortion in therapeutic transplantation research has closed one avenue of promising research directed at the amelioration of Parkinson's disease symptoms, the NIH continues to support other areas of potentially promising research directed at this disease. As already mentioned, NIH is pursuing two alternative research strategies aimed at future therapeutic interventions in Parkinson's disease. One involves the use of implanting placental tissue into the brains of animals to increase the production of dopamine producing cells; the other involves genetically altering rat skin cells so that they secrete dopamine, then implanting the cells into the brains of rats in which dopamine-secreting brain cells had been destroyed.

Mr. Porter. Dr. Wyngaarden also mentioned diabetes research that relies heavily on pancreatic fetal tissue. What is the status of this research? Has diabetes research been restricted due to the Department's policy on fetal tissue?

Dr. Raub. While therapeutic transplantation of human fetal islet cells is prohibited under the current moratorium imposed by the Department, research is continuing along several different tracks to find potential therapeutic interventions for Diabetes.

One focus involves developing alternate mechanical devices, such as a mechanical pancreas, for the delivery of insulin to control blood sugar. Another avenue of research involves genetically transforming cells to activate the insulin production gene within the genome. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) funds thirteen grants and a human islet isolation core that involve the transplantation of adult pancreatic islet cells. The studies focus on attempts to reduce the allogenicity of islet isolation core that involve the transplantation of adult pancreatic islet cells; to utilize growth factors, including fibroblast growth factor (an angiogenic protein); to stimulate islet cell growth; to modify the recipient immune response to islet cell transplants; and to investigate animal models of such transplants. Funds provided for these efforts totalled $2.3 million in FY 1989.

RESEARCH PROJECT GRANTS

Mr. Porter. Please provide for the record a breakout by institute of the percentage of grant applications that are approved and the percentage of approved applications that are funded.

Dr. Raub. The following tables display the percentage of grant applications approved and the percentage of approved applications funded for 1989, 1990 and 1991.

Mr. Porter. Dr. Raub, in your oral testimony you suggested that some members of peer review organizations might approve projects that should not be approved. They do this knowing that these projects will receive such low priority scores that they will never be funded. The apparent motivation for these unmerited approvals is the private sector's reliance on NIH approval in considering privately funded grant applications. This seems an incredible perversion of the grant approval process, particularly given that this committee relies heavily on your statistics regarding the number of approved applications that are funded as a fundamental justification for its funding of NIH extramural research projects.

What are you doing to end the practice of approving unqualified project grants? Doesn't the existence of this practice argue against peer review?

Dr. Raub. My comments regarding the approval and disapproval of applications in study section were made in response to a question by Mr. Natcher. My point was that, on the surface, it might appear that gamesmanship may be at work, but that we rather believe that the increase in approval rates is the consequence of "well prepared people with good ideas." As I stated, we find that competition has grown and as a consequence, "grantsmanship" has certainly improved; those investigators who had a marginal interest in a research career have tended to drop out of the grants system, and primarily the good-to-excellent researchers are left. In addition, due to the current funding difficulties the NIH is experiencing, more and more amended applications are being submitted, which can be expected to be of high quality, having had the benefit of at least one previous critique.

INCLUDES AIDS

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, FY 1989
(DOLLARS IN THOUSANDS)

- Actual -

	DIRECT COSTS ONLY						TOTAL COSTS					
	REVIEWED		COUNCIL RECOMMENDED		COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
NCI	2913	$464,252	2724	$380,636	93.5%	82.0%	2727	$545,210	728	$158,775	26.7%	29.1%
NHLBI	2716	432,912	2498	364,337	92.0	84.2	2504	514,415	698	149,689	27.9	29.1
NIDR	456	55,485	397	46,785	87.1	84.3	410	68,497	109	17,516	26.6	25.6
NIDDK	1913	266,098	1818	215,271	95.0	80.9	1825	317,755	504	92,455	27.6	29.1
NINDS	1556	217,607	1459	175,353	93.8	80.6	1462	252,263	493	83,761	33.7	33.2
NIAID	2165	297,261	2040	240,454	94.2	80.9	2046	347,180	652	113,767	31.9	32.8
NIGMS	2781	331,546	2701	287,744	97.1	86.8	2706	417,745	788	126,965	29.1	30.4
NICHD	1762	241,531	1635	197,792	92.8	81.9	1637	280,157	433	71,557	26.5	25.5
NEI	724	85,830	662	73,582	91.4	85.7	662	105,924	310	45,021	46.8	42.5
NIEHS	378	51,512	363	44,622	96.0	86.6	364	63,110	100	18,124	27.5	28.7
NIA	821	121,029	744	103,238	90.6	85.3	759	155,297	194	38,948	25.6	25.1
NIAMS	702	86,379	657	74,198	93.6	85.9	657	106,596	185	30,544	28.2	28.7
NIDCD	254	31,713	254	30,078	100.0	94.8	254	41,854	97	16,973	38.2	40.6
NCNR	264	40,881	195	26,882	73.9	65.8	199	39,144	50	7,902	25.1	20.2
NCHGR	129	25,430	113	16,938	87.6	66.6	113	25,745	41	10,436	36.3	40.5
TOTAL,NIH	19534	2,749,466	18260	2,277,910	93.5	82.8	18325	3,280,892	5382	982,433	29.4	29.9

NOTE: 1) For FY 1989, the total eligible for funding includes the council recommended for approval plus funded carryover from the prior year.

2) Includes SBIR approved, recommended or funded.

INCLUDES AIDS

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, FY 1990
(DOLLARS IN THOUSANDS)

- Estimate -

	DIRECT COSTS ONLY						TOTAL COSTS					
	REVIEWED		COUNCIL RECOMMENDED		COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
NCI	2980	$518,815	2773	$422,962	93.1%	81.5%	2773	$612,989	766	183,454	27.6%	29.9%
NHLBI	2898	506,380	2728	435,347	94.1%	86.0%	2728	624,601	601	145,513	22.0%	23.3%
NIDR	489	62,756	440	54,323	90.0%	86.6%	440	77,383	90	15,172	20.5%	19.6%
NIDDK	1962	294,375	1877	240,969	95.7%	81.9%	1877	342,286	420	82,545	22.4%	24.1%
NINDS	1567	245,790	1500	196,733	95.7%	80.0%	1500	275,537	471	84,242	31.4%	30.6%
NIAID	2319	391,615	2163	306,892	93.3%	78.4%	2163	431,634	476	99,215	22.0%	23.0%
NIGMS	2825	350,117	2761	306,072	97.7%	87.4%	2761	442,940	637	112,736	23.1%	25.5%
NICHD	1736	263,414	1635	218,045	94.2%	82.8%	1635	303,261	323	59,812	19.8%	19.7%
NEI	664	79,161	594	67,680	89.5%	85.5%	594	96,824	247	38,629	41.6%	39.9%
NIEHS	429	73,522	417	65,280	97.2%	88.8%	417	92,334	99	18,375	23.7%	19.9%
NIA	888	145,900	804	123,804	90.5%	84.9%	804	177,369	156	34,956	19.4%	19.7%
NIAMS	773	99,133	728	87,241	94.2%	88.0%	728	126,253	135	22,511	18.5%	17.8%
NIDCD	312	41,227	299	38,342	95.8%	93.0%	299	53,700	113	21,796	37.8%	40.6%
NCNR	294	42,871	239	30,329	81.3%	70.7%	239	52,023	45	8,480	18.8%	16.3%
NCHGR	189	46,707	185	40,822	97.9%	87.4%	185	62,049	50	15,160	27.0%	24.4%
DRR	55	7,010	50	6,373	90.9%	90.9%	50	9,399	4	749	8.0%	8.0%
TOTAL, NIH	20380	3,168,793	19193	2,641,214	94.2%	83.4%	19193	3,780,582	4633	943,345	24.1%	25.0%

NOTES: 1) For the FY 1990 estimates, the total eligible for funding includes only those applications recommended for approval by the council. The estimates do not include funded carryover from the prior year.

2) Includes SBIR approved, recommended and funded.

INCLUDES AIDS

NATIONAL INSTITUTES OF HEALTH
RESEARCH PROJECT APPLICATIONS REVIEWED AND FUNDED, FY 1991
(DOLLARS IN THOUSANDS)

- Estimate -

	DIRECT COSTS ONLY						TOTAL COSTS					
	REVIEWED		COUNCIL RECOMMENDED		COUNCIL RECOMMENDATION RATE		TOTAL ELIGIBLE FOR FUNDING		FUNDED		AWARD RATE	
	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT	NUMBER	AMOUNT
NCI	2867	$525,739	2700	$435,733	94.2%	82.9%	2700	$631,497	815	186,252	30.2%	29 5%
NHLBI	2915	540,661	2780	477,525	95.4%	88.3%	2780	685,115	718	179,936	25.8%	26.3%
NIDR	523	71,366	479	63,273	91.6%	88.7%	479	90,133	103	18,363	21.5%	20.4%
NIDDK	2004	320,123	1930	264,142	96.3%	82.5%	1930	375,201	495	102,564	25.6%	27.3%
NINDS	1573	266,105	1524	212,861	96.9%	80.0%	1524	298,124	405	70,133	26.6%	23.5%
NIAID	2545	467,334	2381	367,821	93.6%	78.7%	2381	517,329	580	109,293	24.4%	21.1%
NIGMS	3182	420,787	3139	374,170	98.6%	88.9%	3139	541,491	819	151,379	26.1%	28.0%
NICHD	1688	274,504	1611	230,281	95.4%	83.9%	1611	320,280	362	72,378	22.5%	22.6%
NEI	648	79,362	578	69,047	89.2%	87.0%	578	98,779	218	35,315	37.7%	35.8%
NIEHS	424	78,186	417	71,021	98.3%	90.8%	417	100,454	89	16,850	21.3%	16.8%
NIA	967	169,032	900	148,746	93.1%	88.0%	900	213,103	153	38,891	17.0%	18.2%
NIAMS	821	110,987	778	99,394	94.8%	89.6%	778	143,841	150	30,377	19.3%	21.1%
NIDCD	314	45,221	305	42,055	97.1%	93.0%	305	58,900	102	22,383	33.4%	38.0%
NCNR	315	51,124	284	40,099	90.2%	78.4%	284	68,781	33	6,744	11.6%	9.8%
NCHGR	189	51,970	185	45,421	97.9%	87.4%	185	68,820	53	17656	28.6%	25.7%
DRR	--	--	--	--	--	--	46	8,650	--	--	--	--
TOTAL, NIH	20975	3,472,501	19991	2,941,589	95.3%	84.7%	20037	4,220,498	5095	1,058,514	25.4%	25.1%

NOTES: 1) For the FY 1991 estimates, the total eligible for funding includes only those applications recommended for approval by the council. The estimates do not include funded carryover from prior years except for DRR where a new program was established in FY 1990; their unfunded grant applications from the FY 1990 Request for Applications (RFA) are reflected as eligible for funding in FY 1991.

2) Includes SBIR approved, recommended and funded.

I cannot state with certainty that none of more than 2000 reviewers might recommend approval with a knowingly unfundable score, rather than outright disapproval. I agree wholeheartedly that any such gamesmanship, even involving only a few reviewers, is unacceptable. We are constantly on guard against this, and any other irregularity which might undermine the peer review system. The NIH staff responsible for the conduct of study section operations are vigilant in this regard, and the instructions given to reviewers at every study section meeting stress the appropriate use of the recommendations for approval and disapproval.

CHRONIC FATIGUE SYNDROME

Mr. Porter. Last year I asked about Chronic Fatigue Syndrome (CFS). I understand that NIH is conducting primarily basic research and that CDC is looking at the disease from an epidemiological perspective. What can you tell me this year that you couldn't tell me last year, both about scientific advances and your efforts to coordinate research across NIH and CDC?

Dr. Raub. NIAID has conducted studies embodying basic research as well as epidemiological studies and was actually the first to fund epidemiological studies on CFS. Dr. James Jones at the National Jewish Research Center in Denver is completing a 3-year case-control study of CFS and Dr. Anthony Komaroff at Brigham and Women's Hospital and Dr. Dedra Buchwald at the University of Washington have launched the first study to estimate prevalence using a county-based HMO population. The prevalence study has a built-in case-control design which will provide data on risk factors, pre-illness medical history, diagnostic markers and 2-year disease progression. Dr. Komaroff has also just been awarded a second grant to compare multiple sclerosis patients and CFS patients who show the most objective signs of neurologic impairment. The latter is a very comprehensive study which will include neurologic, immunologic and virologic components.

A controlled study in our intramural program involving 40 CFS patients, matched healthy controls, and depressed patients has been initiated. The purpose of the study is to identify an immunologic diagnostic marker for CFS, if one exists, and to determine whether any immunologic features of CFS correlate with overall severity or improvement in symptoms.

The most exciting advance, reported by NIAID investigators, relates to the confirmation of preliminary findings which suggest that CFS patients have neuroendocrine pattern differences when compared to healthy controls and patients with melancholic depression. The neuroendocrine pathway is critical in handling stress and is known to be influenced by a variety of disease processes. These pattern differences may provide a clue regarding the underlying constitutional factors which make CFS patients appear to be more susceptible to allergies, prolonged convalescence from infections, and psychiatric disorders.

Progress is also being made in the development of reagents for identifying specific immunologic defects towards Epstein-Barr virus

(EBV) as seen in some CFS patients and in patients with severe progressive chronic EBV infection.

With regard to coordination of efforts, NIAID intramural scientist, Dr. Stephen Straus, serves as a consultant to the CDC epidemiologic surveillance study as does NIAID grantee, Anthony Komaroff. Drs. John La Montagne and Ann Schluederberg exchange information on studies supported by NIAID with Drs. Lawrence Shonberger, Gary Holmes and Walter Gunn at CDC and encourage collaborations between NIAID grantees and other interested investigators with CDC researchers. The NIAID is also collaborating with the NIAMS on CFS and fibromyalgia, a closely related syndrome.

Mr. Porter. Please describe NIAID's intramural CFS research program.

Dr. Raub. Dr. Stephen Straus in the Laboratory of Clinical Investigation of our Division of Intramural Research continues his pioneering studies of more than one hundred patients with the Chronic Fatigue Syndrome (CFS). His group was among the first to propose and then critically test the idea that the syndrome was caused by the Epstein-Barr virus (EBV). The studies do not confirm the association. In a placebo-controlled clinical trial, acyclovir, a drug which inhibits replication of EBV, was found to be ineffective and a placebo effect was noted in approximately half of the patients. Dr. Straus' group showed that allergies were highly correlated with controlled skin-test reactivities, confirming the widely held perception that atopy, an inherited tendency to develop some form of allergy, is present in a majority of CFS patients.

In small open trials, doxycycline and ranitidine--drugs previously reported by others to be effective--were found to be ineffective in this patient group. Rates of psychiatric disorder were found to be high in CFS cases compared to rates in both the general population and in other chronically ill patient groups similarly interviewed. In an attempt to uncover constitutional differences in CFS patients which might contribute to an increased susceptibility to immune dysfunction and neuropsychiatric symptoms, neuroendocrine studies are currently in progress. The studies have already uncovered novel abnormalities in the infections between the brain and the adrenal gland in patients with CFS. Preliminary data were reported last spring and are nearing publication.

The Institute's current research thrusts are to better define the neuropsychologic and neuroendocrine abnormalities in CFS and to correlate them with immune parameters. This year a major new undertaking was the initiation of a three year study of cellular immune function in CFS patients.

Mr. Porter. NIAID supports CFS research projects at four major medical research centers--Yale University, the National Jewish Center in Denver, Harvard University and the University of Washington in Seattle. Results of these studies will provide important information in CFS. When will these studies be completed, and when will the results be available to this committee?

Dr. Raub. We have four studies in various stages, with the earliest completion date estimated to be December 1990. The last study is estimated to be completed by January 1993. Significant preliminary results are being reported as soon as they are found.

Mr. Porter. How many CFS grants are ongoing through NIH? Please list them.

Dr. Raub. There are four grant awards currently being funded by NIAID to the following investigators:

Dr. George Miller, Jr., Yale University Medical School
Dr. James F. Jones, National Jewish Research Center
Dr. Anthony Komaroff, Brigham and Women's Hospital holds two grants.

Mr. Porter. How many CFS-specific grants were received, approved, and funded for each year FY 1988 - FY 1990?

Dr. Raub. In FY 1988, we received two CFS applications which were approved, but neither were funded because their priority score did not fall into our fundable range. In FY 1989, we received 14 applications of which 13 were approved. One grant was awarded. In FY 1990, we received 11 applications (three of which were transferred to the National Institute of Mental Health), of which 7 were approved. One grant was awarded.

Mr. Porter. Does NIH expect to issue any new grant solicitations in FY 1990 or FY 1991?

Dr. Raub. Solicitations are under consideration for FY 1991 and their issuance will be dependent upon the results of ongoing studies.

Mr. Porter. Last year I asked about new grant solicitations. I was told that no new solicitations were being issued because several long-term CFS studies were already underway. When will these studies be finished?

Dr. Raub. Of the four studies being conducted, the earliest completion date is estimated to be December 1990, and the last study is estimated to be completed by January 1993. Significant preliminary results are being reported as soon as they are found.

Mr. Porter. Last year Dr. Wyngaarden told me of several announcements and Requests for Applications (RFAs) to encourage research that would provide a basis for understanding CFS. What kind of response did you receive to those announcements and RFAs?

Dr. Raub. Thirteen investigators submitted research proposals and there were several resubmissions, bringing the total number of applications received to 27. From the 27 applications received, two awards were made.

AZT AND ddI TRIALS

Mr. Porter. On page 18 of your budget justification, you describe a comparative study of AZT and ddI, treatments for AIDS. When will this study be completed?

Dr. Raub. An NIAID study comparing AZT and ddI began in October 1989 and is still accruing patients, who will take the drug for two years before completing the study. Meanwhile, the Data Safety and Monitoring Board of the AIDS Clinical Trials Group will continue to review the data as they become available. Such interim analyses of the trial data could produce results before the entire trial is completed. However, it is not possible to determine when such an event may occur.

In addition, the Pediatric Branch of the National Cancer Institute has initiated a clinical trial to determine whether there is an advantage to maintaining constant levels of an antiretroviral agent such as AZT in children with neurodevelopmental deficits. Prior studies have shown that there is a highly significant improvement in intellectual and behavioral function in children with AIDS who received AZT by a continuous intravenous infusion. Since this appeared to be of a greater magnitude than the improvements associated with oral AZT, a controlled clinical trial has been designed to evaluate this further. At the same time, due to promising preliminary results obtained with ddI, it was felt important to include ddI in the comparative trial mentioned above. Accordingly, the study just beginning compares oral versus intravenous AZT versus oral ddI. This study will provide important insights about the optimal delivery of an antiretroviral agent as well as the relative benefits of AZT versus ddI. It is expected that data generated from this study will also benefit adults as well as children with AIDS. The study is being performed by the NCI in collaboration with the NIAID and several medical centers. The protocol calls for the accrual of sixty-three patients. Three patients have been enrolled since the protocol opened officially in February 1990.

Mr. Porter. When will the results be available to this committee?

Dr. Raub. We will keep the committee informed of any significant results from these two trials.

Mr. Porter. If ddI compares favorably to AZT in this study, when can we expect to see ddI available to most AIDS patients?

Dr. Raub. If ddI compares favorably to AZT in either of these studies, we have no reason to expect a delay between the finding of drug efficacy and the release of the drug. However, drug availability is basically determined by the pharmaceutical company that produces the drug.

Mr. Porter. You also list a Phase I study of ddI in children. When will this study be complete?

Dr. Raub. NCI's Pediatric Branch initiated a Phase I-II study of dideoxyinosine in children with HIV infection in January 1989. This study, performed at the Clinical Center, has evaluated five dosage levels of ddI. Patients enrolled in this study receive ddI orally on a three times per day schedule. They are monitored closely for clinical and laboratory evidence of drug activity and toxicity. Overall, 73 children have been enrolled to date. Of these, 43 children constitute the core evaluation and there is a minimum of six months follow-up on each of these children. The Pediatric Branch has used ddI prepared by the NCI but has shared all the data accumulated to date with Bristol Myers. In turn, Bristol Myers filed a preliminary report with the FDA in September 1989 and is currently updating this report using an analysis which was completed in January 1990. The Pediatric Branch is conducting its final analysis on the initial 43 patients, since they each completed the minimum six month follow-up in February 1990. These results will be shared with the medical community and will complement the preliminary reports provided to scientists at national and international meetings. It is hoped that these data will provide the basis for a treatment IND for pediatric patients. The results of this study are expected to provide important insights about the role of AZT and ddI in children with AIDS.

In addition, NIAID is evaluating the long-term effects of ddI in children. Patients have been accrued for this study and are being actively followed. Recently, the study period for the pediatric ddI trial was extended to 52 weeks to provide additional data on the long-term tolerance of the drug. At this time, it is not possible to determine when the study will be completed.

Mr. Porter. What is the timetable for proceeding through the next two phases?

Dr. Raub. Based on the results of the Phase I-II study of ddI in children with HIV infection, in February 1990, the Pediatric Branch initiated a Phase II-III study comparing ddI to AZT in children with symptomatic HIV infection. It is estimated that this trial will be completed by 1991.

The next phases of ddI trials support by NIAID are being planned within the context of other important antiretroviral research studies in HIV-infected children. We plan to initiate a new trial of dideoxycytidine (ddC), which will also be made available to children who have failed AZT therapy. This drug has a very different toxicity profile from AZT and ddI and could serve an important role in treating HIV-infected children. It is likely that phase II of the ddI trial will begin in late Summer or early Fall based on the results of our phase I ddI study and that of the NCI.

Mr. Porter. Optimistically, when might ddI be available for treatment of children with AIDS, assuming that results from all three Phases are favorable?

Dr. Raub. Widespread availability of ddI for children with AIDS will depend upon approval of the Treatment IND application by the Food and Drug Administration.

Mr. Porter. Reports in the press this morning indicate that mortality rates for AIDS patients receiving DDI under the expanded access program are 10 times as high as the rates for those receiving ddI under the clinical trials. What effect will this have on the ddI trials at NIH?

Dr. Raub. We are closely monitoring the patients enrolled in our ddI trials for toxicity. Thus far, all patients we have enrolled are still alive. It is likely that the increased mortality seen in the AIDS patients receiving ddI under the expanded access program may have arisen because those patients, who had already failed AZT therapy, were at a much later stage of disease.

INTRAMURAL PROGRAM

Mr. Porter. Please describe the recommendations made in the IOM/NAS study entitled "A Healthy NIH Intramural Program." What steps has NIH taken to implement these recommendations?

Dr. Raub. The Report of the IOM Committee documents the continued excellence of the intramural NIH research programs. While recognizing the hazards in tampering with the structure of a highly successful institution, the IOM Committee recommended changes in six areas that were thought to be necessary for the continued success in a rapidly changing national environment. Recommendations in four of those areas would require Congressional action:

- INCREASED FLEXIBILITY IN PERSONNEL ADMINISTRATION

  The Committee recommended that Congress authorize NIH to develop and implement a personnel demonstration project tailored to overcome the deficiencies of the current system. This area addresses an important problem now facing the NIH intramural program--the substantially inadequate levels of pay for outstanding senior scientists and scientist administrators.

- ENDOWED CHAIRS FOR DISTINGUISHED SCIENTISTS

  The Committee recommended that Congress charter a foundation to permit the private support of up to ten endowed chairs for distinguished investigators.

- DIRECTOR'S DISCRETIONARY FUND

  The Committee recommended that Congress appropriate annually to the Director of NIH an amount no less than $25 million to be used to address emerging issues and special inter-institute research opportunities.

- NIH SCHOLARS PROGRAM

  The Committee recommended that Congress authorize and appropriate funds for an NIH Scholars Program in which outstanding young investigators at the assistant professor level would be appointed on a competitive basis to an independent, non-tenured position in the intramural program.

The NIH drafted a series of legislative proposals that addressed the above recommendations. The FY 1991 President's Budget does include language for the establishment of ten endowed chairs and includes a request for $20 million to establish a Director's Discretionary Fund. Proposals related to increased flexibility in personnel administration, charter of a foundation and an NIH Scholar's program are still under consideration.

Two other recommendations of the IOM Committee would not require legislative action:

- MAINTAINING AN ADMINISTRATIVELY EFFICIENT NIH

  The Committee recommended that the Secretary of the Department of Health and Human Services delegate to the Director of NIH the authority to make decisions on administrative matters without being subject to review by the Office of the Assistant Secretary for Health. The NIH is seeking delegation of further administrative authority to the Director, NIH; this topic has been discussed extensively by a Committee established by the Secretary of HHS to review the position of the Director, NIH.

- IMPROVING THE REVIEW OF THE INTRAMURAL PROGRAM

  The Committee recommended the following actions: (a) A panel chaired by a member of the NIH Director's Advisory Committee should be established to monitor the intramural research program review. (b) Each of the scientific directors and their intramural programs should be reviewed as a whole every four years by an external group. The review report should be submitted to the director of the relevant institute, the NIH Deputy Director for Intramural Research, the Director of NIH, and the Advisory Committee to the Director (ACD), NIH. (c) The Committee recommended that those holding the position of scientific director receive additional compensation.

  The Director, NIH, then initiated a study on "Strengthening the Scientific Review Procedures of the Intramural Research Program" by an ad hoc Consultant Panel to the ADC. The Panel, in responding to the NAS/IOM Report, presented its recommendations and the following conclusions to the ADC on January 26, 1990:

  "This study and the Consultant Panel's recommendations for strengthening the NIH intramural scientific review procedures are in response to the recent review of the NIH intramural program by NAS/IOM.

  "In its report, the NAS/IOM study committee had expressed concerns about whether the review process was sufficient to sustain the future excellence of the intramural program at NIH. The study committee felt that the mechanics of the review process itself were sound, but it framed the issue in terms of what changes could be made to demonstrate that tough questions about the review process were being asked. Concerns about the appointment process for scientific counselors and the procedures for following through on reports by boards of scientific counselors also were expressed by the study committee.

"The NAS/IOM suggested solutions to these issues including enhanced monitoring role for the ACD, and the requirement that the scientific directors and their intramural programs be reviewed by an external body every 4 years.

"The ACD Panel concurred with the NAS/IOM study committee's findings that measures should be taken to strengthen the scientific review process and especially applauded its recognition of the special contributions of the scientific directors to the excellence of the intramural research programs.

"Since its inception, the Director's Advisory Committee, now called Advisory Committee to the Director, has served an advisory capacity on broad science policy matters pertinent to the NIH mission, and the Consultant Panel believes it is appropriate for the ACD to examine and provide its advice periodically on the scientific review procedures of the intramural research program. However, the Panel does not believe that the ACD is the most appropriate body for monitoring the review process and has instead sought to strengthen the existing system.

"The strengthening of the process should occur through the implementation of the Consultant Panel's recommendations. The recommendations include specific means for strengthening the boards of scientific counselors, a more rigorous review and response process based on codified standards, and a more impartial counselor selection process. Finally, the Panel recommended procedures for the periodic review of the scientific and administrative performance of the scientific directors." [From page 23, Report of Consultant Panel to the Advisory Committee to the Director, NIH, December, 1989.]

The Office of Intramural Research is currently revising its policy on "Review and Evaluation of Intramural Research by Boards of Scientific Counselors" (Manual Chapter 3005) to incorporate the recommendations as adopted by the ACD, on January 26, 1990. This process should be completed by the Summer of 1990.

LYME DISEASE

Mr. Porter. What advances have you made in understanding Lyme Disease?

Dr. Raub. The NIAID is actively supporting and encouraging research on all aspects of Lyme disease. Over the past several years our level of support in this area has steadily increased. Some notable achievements resulting from NIAID-supported research are as follows:

- The vector for Lyme disease in the Eastern States is the tick Ixodes dammini, which occurs primarily in the Northeastern States. Until recently, this tick has been considered to be a separate species from Ixodes scapularis, which primarily occurs in the Southeastern States. Research conducted in the laboratories of Dr. James Oliver has demonstrated that ticks are genetically indistinguishable and possess the same physiological potential for serving as vectors for Lyme disease. I. scapularis up to this point in time has not been observed to be a major factor in the transmission of Lyme Disease because in its developing stages it primarily feeds upon lizards and lizards are not competent hosts for the lyme bacterium Borrelia burgdorferi. On the other hand, the developmental stages of its northern counterparts, I. dammini, feed on small mammals, which are competent hosts for the bacterium, as they live in areas with sparse or nonexistent lizard populations. This research indicates that one factor involved in the lower incidence of Lyme disease in the Southern States is the greater presence of lizards which interrupts the life cycle of Borrelia burgdorferi in I. scapularis, an otherwise competent vector of Lyme disease.

- Several laboratories, including the NIAID Rocky Mountain Laboratories, are developing PCR tests for the detection of Borrelia burdorferi in clinical specimens. These tests are still in the developmental stages and will not be ready for general use by physicians in the immediate future. This is new technology that is being applied to a number of diseases. It carries tremendous potential for improving the overall reliability of the diagnostic process.
- The NIAID is increasing its support of research on the pathogenesis of Lyme disease. We have just awarded four new research grants in this area and anticipate that several more awards will be made before the end of this fiscal year. This research is essential for laying the groundwork for new breakthroughs, such as a PCR test, and providing new insights leading to improved therapy of early and late Lyme disease. If an efficacious vaccine is to be developed, it will depend upon the results generated by research in this area.

HEPATITIS

Mr. Porter. Last year Dr. Wyngaarden listed development of an effective therapy for chronic viral hepatitis as one of NIH's achievements. Please describe this therapy. What advances have been made since Dr. Wyngaarden told us about this?

Dr. Raub. In his testimony last year, Dr. Wyngaarden referred to alpha interferon for the treatment of patients with chronic hepatitis B. NIH intramural scientists demonstrated a positive therapeutic effect to alpha interferon for treatment of hepatitis B chronic carriers. After that study, Schering Plough sponsored a multi-center study which showed that about 35% of the hepatitis B chronic carriers who were given 5 million units of alpha interferon for 4 months cleared their hepatitis "e" antigen as compared to 5 percent of those who were not treated. Patients who had lower amounts of hepatitis B virus DNA in their serum responded better to treatment.

Patients who are hepatitis C chronic carriers have also been treated with alpha interferon. Non-specific markers for liver injury became normal in 48 percent or 85 percent of those treated depending upon the study. However, relapse, an indication of ineffective treatment, occurred in over half of the patients who had responded favorably initially. A recent study of ribavirin, a broad spectrum oral antiviral drug, indicated approximately the same level of efficacy as alpha interferon. More work is needed to extend the treatment time, to increase the number of patients studied, and to explore combination ribavirin-alpha interferon therapy.

Mr. Porter. On a related subject, NIH is also developing a vaccine for the Hepatitis A Virus (HAV). Have you begun testing human volunteers yet? If not, when will the human testing begin?

Dr. Raub. The clinical study for evaluating the live, attenuated hepatitis A vaccine developed by NIAID intramural scientist Dr. Robert Purcell began in late January of this year. The purpose of the study is to determine the vaccine's safety and immunogenicity as well as determine an adequate infective dose when administered orally.

Mr. Porter. When will the testing be completed?

Dr. Raub. Depending upon initial results on the vaccine's safety and antibody response, current plans are to expand the number of volunteers involved in the study. Since the study uses escalating doses and hence has different start dates, it may take up to a year to administer all the doses and up two years to complete this first study in humans.

HYPERTENSION

Mr. Porter. NIH is conducting a large study on marginal hypertension. When will this study be completed? What do your early findings show regarding what types of drugs are effective, and how effective are they?

Dr. Raub. The study to which you are probably referring to is the Treatment of Mild Hypertension Study (TOMHS). The pilot study for this larger clinical trial will continue through Fall of 1990. The large clinical trial was not recommended for funding by the National Heart, Lung and Blood Advisory Council. The trial was estimated to cost as much as $240 million over 10 years, and the Council felt such a large project would adversely affect the resources available to other investigator initiated research. The investigators have applied for support to continue the pilot study for an additional two years.

The drugs being studied in this pilot study represent five different classes of antihypertensive agents: diuretics (chlorthalidone), beta-blockers (acebutolol), alpha-antagonists (doxazosin), calcium-antagonists (amlodipine) and angiotensin-converting-enzyme inhibitors (enalapril). The results to date indicate that when combined with nutritional treatment, all five drugs are safe and effective to similar degrees. They do not differ significantly in terms of blood pressure (BP) reductions, all lowering diastolic BP by 4 to 6 millimeters of mercury more than nutritional treatment alone (given with placebo pills). With the low doses given, there are few differences in symptomatic side effects attributable to any of the drugs. Data regarding possible differential effects on various measurements of cardiac structure and function are still being collected and analyzed.

DISEASE TREATMENT

Mr. Porter. NCI has taken the lead in collecting tropical forest plants to investigate their potential use in treating AIDS and cancer. This is a highly commendable initiative. Shouldn't it be expanded to include the other institutes so that plants may be collected and tested for their potential usefulness in treating a wide range of disorders?

Dr. Raub. Over 6,000 extracts of over 15,000 tropical plant samples collected in the current program have been submitted for testing in the AIDS-antiviral screen, and over 600 have exhibited some preliminary *in vitro* activity. Over 100 of these extracts are in various stages of fractionation, and several new classes of *in vitro* anti-HIV active compounds have been isolated. It should be stressed, however, that the observed activity is *in vitro*, and extensive *in vivo* testing, preclinical and clinical studies will be necessary before any claim to true efficacy can be made.

Plant samples representing 310 families and over 1,650 genera have been collected thus far. Examples of some of the families are Acanthaceae, Annonaceae, Apocyanceae, Burseraceae, Euphorbiaceae, Fagaceae, Meliaceae, Myrtaceae, Sapindaceae, and Verbenaceae. Genera include *Dregea, Holarrhena, Canarium, Brevnia, Lithocarpus, Dysoxylum, Syzigium, Blighia* and *Vitex* from the families listed above. Specific species are *Dregea sinensis, Holarrhena antidysenterica* and *Vitex gaumeri.*

In view of the preliminary nature of the present studies, NCI does not publicize which plants have shown *in vitro* activity. Such publicity might promote the spread of misleading information as to the true effectiveness of the plant, and could also result in depletion of valuable resources by people desperate for treatment, not to mention the potential that they may suffer severe toxic side effects.

Testing in the anticancer cell line screen is starting, but it is still too early to give meaningful statistics. While the plants might be tested for a range of other bioactivities, the size of present NCI collections only provides sufficient material for anticancer and anti-HIV screening, and some preliminary fractionation of active extracts.

BONE AND MINERAL DISEASE

Mr. Porter. Dr. Raub, I am interested in the level of NIH supported research in the are of bone and mineral disease. I understand that a number of Institutes--NIA, NIAMS, NIDDK, NICHD, NIA, NIDR, and of course NIAMS---may be involved in research in this area. Could you please provide for the record a summary of NIH supported research on bone and mineral disease by Institute in the following areas: Osteoporosis, primary hyperparathyroidism, steroid, induced bone disease, Hypercalcemia of malignancy, Paget's disease, Nephrolithiasis, bone disease associated with renal failure (renal osteodystrophy), Neonatal hypocalcemia, Vitamin D deficiency rickets (and other rickets research), genetic disorders resulting in bone disease, and finally calcium disorders resulting in bone disease. For each of these areas, I would appreciate knowing which Institutes are actively involved in the research effort, and what level of funding has been allocated to these initiatives.

Dr. Raub. As the lead agency for bone biology and bone diseases, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports many grants in these areas. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) provides major support for research on nutrition, on the relationships among hormones regulating bone metabolism, and on the fundamental mechanisms responsible for maintaining body calcium homeostasis, as related to osteoporosis. All of these studies are critical to understanding the pathogenesis of osteoporosis and ultimately to designing effective strategies for its prevention and therapy. The National Institute of Child Health and Human Development (NICHD) supports a variety of studies concerning bone and mineral disease of which a majority is concentrated in the area of genetic disorders. Some of these studies utilize mutant limb animal models and transgenic animal models to correlate the biochemical defects with the abnormal function at the molecular and genetic level.

The following tables provide the specific information requested for each ICD involved in FY 1989 and a summary estimate for FY 1989-1991. These basic research efforts are the underlying science from which future applied advances may be developed. As some projects are applicable to more than one category, they are counted more than once, and thus the table does not add to the total program in this area. Also, please note that the categories requested are not inclusive of the entire portfolio of basic research projects that address bone metabolism, growth and structure.

Mr. Porter. Is there any data indicating the frequency of these various bone and mineral diseases, or their economic impact?

Dr. Raub. Data on the frequency and economic impact of bone and mineral diseases is not uniformly available. The following is the best available data for the diseases that you mention.

Osteoporosis, a condition in which bone mass is reduced and there is an increased susceptibility to fractures, is a major public health problem in the United States. It effects more than 24 million people in the U.S. and is responsible for at least 1.3 million fractures each year, typically fractures of the spine, wrist, and hip. The direct and indirect costs of osteoporosis in the United States have been estimated to be $7 to $10 billion annually.

Osteoporosis affects over twenty million people in the U.S. including one-half of women over 45 and 90 percent of those over age

75. One-third of women over 65 years of age suffer spinal fractures; one-third of women and one-sixth of men will suffer a hip fracture by the time they are 90. Of the 227,000 hip fractures that occur in the U.S. every year, almost 50 percent are suffered by persons 80 years of age or older. There is an alarming 12 to 20 percent mortality rate from hip fracture and 20 percent of the survivors will be admitted to nursing homes, often for the rest of their lives.

In addition to the toll of pain and suffering, osteoporosis causes a tremendous drain on health care resources. Hip fractures alone account for over $7 billion annually. A savings of $5 billion could be realized by reducing the present overall fracture rate by one-half. Furthermore, if present trends continue, the cost of medical care for hip fracture in thirty years will increase from $7 to $30 billion per year. A 50 percent reduction in these expenditures would be $15 billion per year.

Primary hyperparathyroidism: Hyperthyroidism is a well recognized risk factor for osteoporosis. Recently NIDDK grantees have found that thyroid hormone administration may predispose patients to develop osteoporosis. Long-term thyroid hormone therapy is associated with a 10 to 12 percent decrease in hip bone density in premenopausal women. Since thyroid hormone use is very prevalent, a large number of women may be at risk for osteoporosis. In this regard, NIDDK grantees have developed improved tests to monitor the dose of thyroid hormone needed. Awareness of the potential adverse effects of excessive thyroid hormone and careful monitoring of patients on therapy may significantly lessen their risk. Approximately 0.5 percent of the U.S. population is affected by primary hyperparathyroidism.

No data are available on the frequency of steroid induced bone disease, hypercalcemia of malignancy, bone diseases associated with renal failure (renal osteodystrophy), neonatal hypocalcemia, vitamin D deficiency rickets disease (and other rickets research),

Paget's Disease: No current figures are available on the frequency of Paget's disease in the United States. However, surveys in England and Germany have provided estimates of the prevalence rate of Paget's disease in individuals over forty years of age to be approximately 3 to 4 percent.

Nephrolithiasis: An estimated 4 percent of the U.S. population will experience nephrolithiasis (kidney stones) in their lifetime.

Genetic Disorders Resulting in Bone Disease: Congenital malformations of the musculoskeletal system are diagnosed among live births and stillbirths more frequently than defects of any other organ system. Estimates of prevalence rates for all musculoskeletal conditions diagnosed at birth range from 3 to 10 percent depending on whether minor anomalies are counted as well as major abnormalities. The causes of many of these conditions are unknown.

Osteogenesis imperfecta is one of the known genetic disease of children causing fragile bones with premature bone fractures, and additional defects in other organs that consist largely of connective tissues. As estimated 30,000 people in the United States are afflicted with osteogenesis imperfecta.

Calcium Disorders Resulting in Bone Disease: Other disorders of bone and mineral metabolism have been identified. These include, Legg-Calve-Perthes disease, osteopetrosis and pediatric osteoporosis. However, estimates of their frequency are not available.

JUSTIFICATION OF THE BUDGET ESTIMATES

Department of Health and Human Services
Public Health Service
National Institutes of Health

FY 1991 Congressional Justification
Overview

I. Introduction

The National Institutes of Health (NIH) is the principal biomedical research agency of the Federal Government. Through the conduct, support and promotion of biomedical research, NIH seeks to improve the health of the American people by: increasing the understanding of the processes underlying human health, disability, and disease; advancing knowledge concerning the health effects of interactions between man and the environment; developing methods of preventing, detecting, diagnosing, and treating disease; and disseminating research results for critical review and ultimately for medical application. In the pursuit of this mission, NIH supports biomedical and behavioral research in this country and abroad, conducts research in its own laboratories, trains promising young researchers, and promotes the acquisition and distribution of medical knowledge. These research activities uncover new ways to prevent and ameliorate disease and disability, seek to lessen the enormous economic and human toll exacted from the Nation, and lead to better health care for the American people. In addition, the basic research and research training programs supported by the NIH have provided the foundation for the development of this Nation's growing biotechnology industry and continues to be its principal impetus. The investment by the Federal Government through the NIH has made the United States preeminent in this field.

II. Fiscal Year 1990 Budget Policy

The FY 1990 Appropriations Act for the Departments of Labor, HHS, and Education (P.L. 101-166), provides the NIH net appropriations of $7,672.9 million. As required by the Appropriations Act, this amount reflects the following adjustments:

- A $10.0 million reduction to reflect the limit on the use of appropriated funds to pay the salary of an individual through a grant or contract at a rate in excess of $120,000 per year;
- A $4.0 million reduction to be achieved as a result of improved procurement practices; and
- A $10.4 million reduction representing the NIH share of the $15 million DHHS reduction in the amounts appropriated for salaries and expenses.

In addition to these adjustments, the FY 1990 level reflects a reduction of $96.6 million from the appropriated amounts as a result of sequestration as required by the Omnibus Budget Reconciliation Act of 1989. The sequestered amount represents an across-the-board reduction of approximately 1.4 percent against all budget authority appropriated to NIH in the FY 1990 Appropriations Bill. This 1.4 percent reduction has been applied against the appropriation of each NIH component as well as against each program, project, and activity. The following table summarizes all of these adjustments.

FY 1990 Appropriations	$7,697,350,000
- Less Extramural Salary Cap Reduction	-10,000,000
- Less Procurement Reduction	-4,000,000
- Less Salaries and Expenses Reduction	-10,428,000
FY 1990 Net Appropriations	7,672,922,000
Less Sequestration Amount	-96,570,000
FY 1990 Budget Authority	$7,576,352,000

The FY 1990 funding level of $7,576.4 million represents an increase of 6.0 percent or $431.5 million over the FY 1989 comparable level of $7,144.9 million. Included in the FY 1990 funding level is $743.5 million for AIDS, an increase of $141.9 million and $59.5 million for the Human Genome Program, an increase of $31.3 million.

The FY 1990 budget level will support 13,779 full-time equivalent (FTE) positions as allocated by the Secretary, DHHS. This is an increase of 565 FTEs (380 non-AIDS FTEs and 185 AIDS FTEs) over the FY 1990 President's Budget. When compared to the FY 1989 level of 13,204 FTEs, this level represents a net increase of 575. The increase will enable NIH to continue to staff new initiatives and to enhance the responsible management of the NIH programs.

The FY 1990 budget for research project grants (RPGs) would fund approximately 20,316 total grants at $4,198.0 million. Included in these totals is $289.6 million to support 734 AIDS grants and $40.3 million to support 144 human genome grants. The total number of grants includes 15,683 noncompeting and 4,633 competing awards. The FY 1990 level would provide average cost increases of 4.1 percent for noncompeting and 11.5 percent for competing awards. Downward negotiations would approximate 11 percent for noncompeting and 13 percent for competing research project grants.

The FY 1990 level for research training would support 11,795 trainees for a total of $286.7 million. This is an increase of 570 trainees over the 1989 level of 11,225. Included in this increase is an additional 9 trainees for AIDS and 135 trainees for human genome research. Excluding these two programs, the FY 1990 level for research training represents an increase of 426 trainees over FY 1989.

Because of the high priority given to the research career program, this program will be increased by 12.2 percent for a total of $104.9 million. This increase will provide for an additional 67 research career awards.

In the aggregate, the other extramural funding mechanisms, with the exception of AIDS and the Human Genome Program, will be funded at approximately the FY 1989 program level. The efforts in AIDS and the Human Genome Program have been enhanced. The Biomedical Research Support Grant Program, which had been proposed for elimination in the FY 1990 request, will be supported at a level of $44.4 million.

The FY 1990 budget for construction is $16.3 million. Included in this amount, in accordance with the FY 1990 Appropriations Act, is $14.8 million for extramural facilities construction grants. These funds have been set aside within the appropriation of each of the individual NIH institutes pending the review of construction grant applications and subsequent funding decisions. Also included within the construction mechanism is $1.5 million for the NCI for the repair and improvement of facilities at the Frederick Cancer Research Facility.

The NIH in-house activities will receive increases over the FY 1989 level to cover built-in increases. The cost of the January 1990 pay raise has been funded.

Included in the appropriation of the Office of the Director is $33.5 million to support the purchase of an upgraded state-of-the-art supercomputer necessary to support the science base at NIH and the National Cancer Institute's Advanced Scientific Computing Laboratory. Also included is $2.0 million to establish an intramural research program for diagnostic radiology.

The NIH Buildings and Facilities (B&F) account will be funded at a level of $61.0 million. This amount will provide for the following projects:

Clinical Center Modernization/Safety	$1,800,000
Upgrading of Animal Facilities	5,300,000
Child Health and Neurosciences Facility (Phase 3)	33,000,000
Addition for NIEHS Facility (to complete design)	20,000
AIDS Construction Projects	14,765,000
Routine Repairs and Improvements	6,157,000
Total	61,042,000

III. Fiscal Year 1991 Budget Policy

The FY 1991 budget request for the NIH favors basic research and totals $7,929.7 million, an increase of $353.3 million or 4.7 percent over the FY 1990 level. Included in this funding level is $800.2 million for AIDS, an increase of $56.6 million or 7.6 percent. Also included is $108.0 million for the Human Genome Program, an increase of $48.5 million or 81.4 percent. The FY 1991 request continues to reflect the priority the Administration places on the support of basic research. In addition, the budget includes, for the first time, a separate request for the new National Center for Human Genome Research, established in FY 1990.

As a reflection of the importance NIH places on expanding the number of biomedical researchers who are ethnic minorities, the FY 1991 budget requests that the Minority Access to Research Careers Program, the Minority Biomedical Research Support Program, the Minority High School Student Apprenticeship Program, and the Research Centers in Minority Institutions receive an overall 17.0 percent increase over FY 1990.

The budget request includes 14,133 FTEs, an increase of 354 over the FY 1990 level of 13,779. Included in this increase is 243 non-AIDS FTEs and 111 AIDS FTEs as allocated by the Secretary,DHHS. The additional FTEs will enable NIH to continue additional activities undertaken in FY 1990 and provide support for expansions in the AIDS program, the Human Genome Program, and the minority assistance programs.

In allocating the FY 1991 request by mechanism, NIH gave its highest priority to the support of its intramural infrastructure funded under Buildings and Facilities (B&F). NIH facility needs have become critical because adequate attention has not been given to them in recent years. Of particular importance is continued support for the ongoing Clinical Center Modernization/Safety and Laboratory Buildings Renovations Projects. Less than $2.0 million in new funds has been available for Clinical Center modernization since FY 1987, and no additional funds have been available for laboratory buildings renovations since FY 1988. These projects have been continued with funds carried-over from prior years. Our intramural animal facilities are also in urgent need of upgrading. At this time, NIH would not be able to comply with the minimum specification standards for animal facilities that it has encouraged for NIH grantees. In addition, the condition of the NIH infrastructure - its boilers, chillers, steam lines, etc., - have reached the critical point where their useful life is ending. A long term modernization program must be begun before there is a failure of these systems.

The NIH firmly believes that these facility needs must be addressed; and, therefore, has requested $88.6 million for B&F. The individual projects and the funds requested for them in FY 1991 are indicated below.

Laboratory Buildings Renovations	$13,000,000
Clinical Center Modernization/Safety	14,500,000
Upgrading of Intramural Animal Facilities	18,500,000
Upgrading of Infrastructure	19,200,000
Routine Repairs and Improvements	6,900,000
AIDS Construction Projects	16,500,000
Total	88,600,000

Equally important is the need for repair and improvement of facilities at the Frederick Cancer Research Facility. An additional $1.5 million has been requested in the construction mechanism for this purpose.

Investigator-initiated research continues to be a very high priority of the NIH. The FY 1991 request will support a total of 20,439 research project grants, 123 more awards than in the FY 1990 level. Included in this increase are 26 awards for the Human Genome Program and 118 grants for AIDS. These increases are offset by a slight reduction of 21 awards, in other areas, from the FY 1990 level.

Research project grants would be funded at a level of $4,424.8 million, an increase of 5.4 percent over the FY 1990 funding level. This amount will allow average cost increases of about 5.8 percent for noncompeting and 2.0 percent for competing awards. The request will support 5,095 competing RPGs, including 239 AIDS awards and 53 human genome research awards. This is an increase of 462 competing awards from the FY 1990 level. The outyear commitments generated by the competing grants funded in FY 1991 plus the noncompeting continuation grants, which have commitments in FY 1992-1995, total approximately $10 billion over this four year period.

Historically and in the normal process of grants administration, noncompeting and competing research project grants have been reduced by about 1 and 3 percent, respectively, from committed amounts and study section recommended levels. However, in recent years, the NIH has not been able to fund its grants at these historical levels. This trend will continue in the FY 1991 request. Downward negotiations in the FY 1991 request will approximate 10 percent for noncompeting and 14 percent for competing awards.

The FY 1991 budget reflects the continuation of the FY 1990 policy to limit the use of appropriated funds to pay the salary of an individual through a grant or contract at a rate in excess of $120,000 per year.

Research training serves to replenish the Nation's corps of biomedical research investigators. It takes many years to develop high quality researchers, and the level of training supported today determines our research capability in the future. Therefore, the NIH continues to place a high priority on research training. The FY 1991 request will support a total of 12,020 trainees, an increase of 225 trainees over the FY 1990 level of 11,795. Included in this increase is 136 trainees for the Minority Access to Research Career (MARC) Program and 89 trainees for the Human Genome Program. There are no stipend or tuition increases included for FY 1990 or FY 1991.

Excluding AIDS, the minority programs, the Human Genome Program, and extramural construction; most of the other extramural funding mechanisms will be supported at levels equal to the FY 1990 dollar level. The R&D contracts mechanism includes $4.0 million for the first year costs of a pertussis clinical trial and for expanded basic research on a pertussis vaccine. In the aggregate, AIDS research supported under the other extramural funding mechanisms will increase slightly over the FY 1990 program level.

The BRSG program is one of three activities in the Biomedical Research Support Program funded by the Division of Research Resources. The objective of the BRSG program has been to strengthen and enhance the research environment of institutions heavily engaged in health-related research. The most common use of these funds has been for small pilot projects and for interim funding between grant-supported projects. In view of the continuing emphasis on investigator-initiated research as the most appropriate form of support, the BRSG program has been given lower priority when compared to other programs that permit the directing of research funds to specific target areas. In FY 1991, the BRSG program will be funded at a level of $17.7 million. Consistent with the Secretary's minority health initiative, one third of the FY 1991 funds will be awarded to institutions to increase support for underrepresented minorities or economically disadvantaged students. This Program will assist in the national mission to increase the number of women, underrepresented minorities, economically disadvantaged people and others in science and engineering.

The Intramural Research Program at NIH is the Nation's preeminent institution for biomedical sciences. The excellence of NIH scientists and the exceptional intramural facilities, including the Clinical Center and Ambulatory Care Research Facility (ACRF), afford many research opportunities that cannot be duplicated elsewhere. The request for intramural research of $914.9 million provides an increase for intramural research of 6.9 percent over the FY 1990 base. This increase will allow for continuing expansion in the AIDS program and will cover the costs of such administrative items as within-grade increases. Funds have also been included for one-half of the cost associated with a January 1991 payraise of 3.5 percent.

The request for Research Management and Support and the in-house activities supported by the Office of the Director and the National Library of Medicine also includes funds over FY 1990 to provide for built-in increases.

The request includes $20.0 million for the establishment of a NIH Director's Discretionary Fund. Although Congress did not include support for this fund in the FY 1990 appropriations, NIH believes it is an important mechanism that will allow the NIH to be more responsive to emerging research opportunities and health priorities.

NIH is continuing its initiative to improve its procurement of small purchases. Additional savings are being realized by individually negotiating the purchasing agreements of high volume vendors and through use of consolidated purchases wherever feasible. The FY 1991 budget request assumes additional savings of $3.2 million above those generated in the previous two years. Additionally, NIH is reorganizing its delegated procurement structure, which will reduce the number of staff authorized to place orders by 66 percent and the number of ordering offices by 36 percent. Also, as part of the reorganization, the use of full-time purchasing agents has been emphasized in order to build a more qualified professional purchasing staff. To that end, NIH has established an extensive small purchases training program, which includes a series of advanced procurement seminars and a unique procurement awareness course for scientific staff.

The budget proposes to give the NIH Director the discretion to direct up to one percent of NIH appropriations to emerging activities.

Additionally, the budget proposes to implement a recommendation of the Institute of Medicine to create ten endowed chairs. These chairs, supported through Federal funds and private donations, would support term appointments of distinguished scientists at NIH.

IV. Program Evaluation

Section 2611 of the Public Health Services Act authorizes that up to one percent of funds appropriated for programs authorized by the Act may be used for program evaluation. Until FY 1987, the program evaluation program totalled approximately $14.5 million for studies conducted by the Office of the Secretary, the Office of the Assistant Secretary for Health, and the NIH. In FY 1987, the Congress directed that these funds also be used to support the National Medical Expenditure Survey and in FY 1988 the National Health and Nutrition Examination Survey. In FY 1990, the Congress, through the Omnibus Budget Reconciliation Act established the Agency for Health Care Policy and Research authorizing the use of up to 40 percent of the one percent set-aside funds for its support. The NIH estimates that $53 to $60 million will be assessed for the one percent set-aside in FY 1990 compared to $14.5 million in FY 1986. The funds to support the one percent set-aside come primarily from funds appropriated for research grants and contracts.

V. Acquired Immunodeficiency Syndrome (AIDS)

FY 1991 will mark NIH's tenth year as a major contributor to the Nation's fight against AIDS. During the past decade, many advances have been made. Detailed descriptions of the AIDS research conducted and supported by the various NIH components are contained within the individual budget justifications and in the summary section entitled AIDS.

The AIDS program is the largest trans-NIH research effort and has coordination and direction through the Office of AIDS Research, the AIDS Executive Committee and the AIDS Program Advisory Committee. Nineteen components of NIH participate in the AIDS effort. This extensive involvement draws upon the unique strengths and capabilities that are embodied in both the intramural and extramural components of the NIH.

The FY 1991 funding request for AIDS is $800.2 million. This is a 7.6 percent increase over the FY 1990 estimate of $743.5 million. The NIH plan for the AIDS program was developed in recognition of the fact that flexibility must be maintained. In essence, the unfolding scientific realities of AIDS will play the leading role in shaping the scope of overall efforts and in determining the extent of which future research plans will evolve.

VI. Human Genome Initiative

On October 1, 1989, the Secretary of Health and Human Services established the National Center for Human Genome Research, combining the functions of the Office of Human Genome Research, a planning and coordinating unit in the Office of the Director, NIH, and the human genome grants and contracts management previously provided by the National Institute of General Medical Sciences. The Secretary gave the center the mission of achieving the national objective to determine the human DNA sequence.

Gene mapping and DNA analysis will be key tools for biology in the 21st century. When finally interpreted, the genetic messages encoded within our DNA molecules will give us the basic instructions for the chemical foundation of human existence. By determining the location and structure of specific genes on the 23 pairs of human chromosomes, scientists will gain valuable tools to use in their quest to understand and eventually treat many of the more than 4,000 single-gene diseases that afflict mankind, as well as the many multifactorial diseases in which genetic predisposition plays an important role. The information generated will have a profound impact on many fields of science and technology. A more important set of instruction books will never be made available to human beings.

During FY 1990, a five-year plan for the Human Genome Project was developed jointly by the National Institutes of Health (NIH) and the Department of Energy (DOE) in consultation with the NIH Program Advisory Committee on the Human Genome and the DOE Health and Environmental Research Advisory Committee (HERAC). This plan outlines specific scientific goals for the period FY 1991 through FY 1995, as well as the plan for managing the program so that the goals can be met.

The FY 1991 budget request includes a significant increase for the National Center for Human Genome Research, continuing the emphasis placed on the Human Genome Initiative by the Administration and the Congress. The FY 1991 request for the NCHGR is $108.0 million. This amount represents an increase of $48.5 million or 81.5 percent over the comparable FY 1990 estimate. A total of 170 research project grants are estimated for support in FY 1991, including 53 competing awards. The center estimates that an additional 6 center grants will be supported for a total of 9 center grants at a level of $35.7 million. The center also estimates support for 224 full-time permanent trainee positions, 12 research career awards, 18 conference and other related research awards, and 5 research and development contracts.

VII. Scientific Advances

This overview highlights recent scientific advances resulting from biomedical research conducted at or supported by the National Institutes of Health (NIH). These selected achievements illustrate both basic and targeted research in six areas: human genome, biotechnology, neurobiology, AIDS, clinical trials, and vaccines. A final section discusses additional selected advances.

HUMAN GENOME RESEARCH

On October 1, 1989, the NIH created a new component, the **National Center for Human Genome Research (NCHGR)**, to be the focal point for its human genome research. This new administrative entity will do much to insure a well-planned and closely coordinated effort across the NIH and between the NIH and the Department of Energy (DOE).

During the past year, several advances significantly improved the technology used to map and sequence DNA:

- New Approaches to DNA Sequencing. New methods to improve the rate and cost effectiveness of DNA sequencing (determining the relative order of base pairs, the building blocks of DNA), including automation, are currently being investigated. In the past 2 years, the cost of sequencing DNA under optimal conditions has been reduced from $5 per base pair to approximately $2 per base pair. Since there are perhaps 3 billion base pairs in the human genome, the cost of sequencing must be reduced to well below $1 per base pair before large-scale projects, such as the complete sequencing of human DNA, are undertaken. Sequences of short stretches of DNA (both human and other organisms) will, of course, continue to accumulate as a by-product of many research projects; currently about 10 million base pair sequences are determined in this way each year.

- Maps and Sequences of Model Organisms. Genome maps and DNA sequences of important model organisms will be essential for the interpretation of human DNA sequences. The physical map of the DNA of the yeast, *Saccharomyces cerevisiae*, and the round worm, *Caenorhabditis elegans*, have been refined sufficiently to make sequencing of these DNAs feasible.

- GenBank, a database of sequence information is now available to scientists online so that they can get up-to-date information on a daily basis. Comparing new sequence information to other known DNA sequences is an important step in unravelling the function of newly discovered genes.

- More Markers and Genes Located. The number of identifiable markers (an easily recognizable feature, such as a particular segment of DNA, the inheritance of which can be monitored along with that of the gene of interest) located within the human genome was reported to have increased from 2,057 to 4,362. Similarly, the number of mapped human genes rose from 610 to 945.

- Vectors are biological vehicles, such as the DNA of a virus or bacterium used to isolate, clone, and transport the DNA of interest into a host organism. Yeast artificial chromosomes (YAC) are vectors that allow cloning of DNA fragments 2 to 20 times larger than those cloned using conventional vectors. Physical map construction is simplified when high capacity vectors are employed because large DNA fragments yield results that are easier to interpret than those from numerous smaller ones. Work with YAC vectors has recently been facilitated by the application of a new technique called polymerase chain reaction (PCR) that recognizes clones containing a specific gene or DNA marker (see below for a discussion of PCR). A number of genes and markers on the human X chromosome have been mapped using these techniques.

As new techniques are developed under the auspices of the genome program, they will be used in the course of research on genetic diseases supported by the categorical institutes of the NIH.

Research on human and animal genes is under way through almost every NIH component. A few recent examples of successful gene isolation are discussed below.

- Cystic Fibrosis Gene. The cystic fibrosis (CF) gene, present in 1 out of 20 Caucasians, is one of the most commonly carried disease genes in the general population. One of the most exciting research events of the year was the announcement that this gene had been isolated on chromosome number 7, a finding that offers renewed hope to the 30,000 CF patients likely to die in childhood or early adulthood from the devastating effects of this disease. Scientists will now be able to produce for study large amounts of the defective protein that causes the disease. When that research gives rise to expanded knowledge about the disease mechanism, scientists may be able to develop new, more effective treatments and, eventually, to replace the affected gene. Inexpensive CF diagnostic screening tests (currently tests are very expensive) also may be available soon to identify CF carriers.

- Melanoma and Dysplastic Nevi Gene. Approximately 10 percent of all melanomas (malignant tumors of pigment cells, such as those located in the skin) occur in individuals with a family history of melanoma, and about half of all melanomas arise in the 5 to 8 percent of the general population who have dysplastic nevi (benign pigmented precursor lesions). Persons with dysplastic nevi have a sevenfold increased risk of developing cutaneous melanoma. The gene associated with familial forms of melanoma and dysplastic nevi was recently located on chromosome 1. Further research will reveal whether probes (a single strand of DNA used to seek out its complement) can be developed to identify those at high risk for a melanoma.

- Mapping Other Genes of Interest. Significant progress has been made in mapping a number of other disease-related genes. The search for the gene for **neurofibromatosis** (a disorder producing pigmented irregularities, skin and nerve tumors, and subcutaneous and bony deformations) has been accelerated; research indicates that it is a very large gene like that for Duchenne muscular dystrophy. Numerous gene mutations in mice cause hereditary hearing loss; among these mutant mice, one particular strain, the *Bronx Waltzer*, is yielding important information on genetic deafness and may serve as a model of the human condition. The gene involved in multiple endocrine neoplasia type 2A, an inherited disease typified by the development of thyroid, parathyroid, and adrenal gland tumors, has been mapped to chromosome 10. The chromosomal loci for several bone matrix proteins that may be involved in connective tissue diseases such as osteoarthritis, osteoporosis, and osteogenesis imperfecta also have been mapped. The gene encoding the human alpha B-crystallin gene has been sequenced and mapped to chromosome 11; in the lens, crystallins are structural proteins important for clear vision, wherein other body tissue, they are expressed as metabolic enzymes.

- Muscular Dystrophy Cell Transplant Technique. Gene isolation frequently opens new research opportunities. A good example is the acceleration in Duchenne muscular dystrophy research since the discovery and cloning of the gene responsible for this crippling, ultimately fatal degenerative disease of young boys. Most recently, scientists have transplanted normal muscle precursor cells into mice genetically deficient for dystrophin, the protein absent in Duchenne muscular dystrophy. The transplanted cells fused with the deficient muscle fibers and produced dystrophin. In a different mouse model, dystrophic animals that received cell transplants showed improvement in their symptoms and lived longer than control animals. Preliminary steps are under way to test cell transplant techniques in human patients. Duchenne type muscular dystrophy effects 1 in every 3,500 live male births.

As scientists devise methods to understand DNA's structure and function, the resultant techniques continue to fuel a new biomedical discipline, biotechnology.

BIOTECHNOLOGY

Laboratory techniques for selectively cutting and recombining DNA, fusing specific cells to produce monoclonal antibodies, and manufacturing synthetic peptides have a broad range of applications. For instance, recombinant DNA techniques are used to develop new drugs and diagnostic kits, to produce plants resistant to diseases or herbicides, and to clean up the environment. At the same time, these techniques continue to be of profound importance in biomedical research. In this section, examples of recent biomedical applications are provided.

- Structure of Blood Clotting Proteins. Attempts to produce biologically significant proteins through the use of biotechnology do not always succeed because, while biologists can engineer genes to produce proteins, they often do not fold into the precise three-dimensional configurations required to make them function properly. Recently the three-dimensional structures of thrombin and platelet factor 4, two proteins involved in blood clotting and hemostasis, have been determined. There is great interest in developing clinically useful inhibitors of thrombin because uncontrolled clotting by this "killer enzyme" is a major factor in approximately 40 percent of all deaths. Platelet factor 4, on the other hand, has significance even beyond blood coagulation because it belongs to a class of proteins involved in both wound healing and uncontrolled cell growth leading to cancer formation.

The ability to reproduce these proteins in their precise three-dimensional configurations should eventually lead to resolutions of such problems.

- Stabilizing Biological Molecules. Proteins can be used for many commercial purposes, including cleansers and pharmaceuticals. One major practical difficulty in such applications is their frequent instability, both when exposed to high temperatures or other adverse environmental conditions, and when being naturally processed and "degraded," or broken down, inside cells. Although many investigators have worked on this problem, no one until recently has been able to determine which proteins will be more stable than others and why, much less how to control their stability. Within the past year, techniques have been developed to determine how various types of interactions (e.g., hydrogen bonds, hydrophobic interactions, and salt bridges) contribute to quantitative and qualitative protein stability. These techniques are expected to be of great value to scientists trying to stabilize biological molecules used in medicine (e.g., vaccines) and to design improved enzymes for use in the pharmaceutical and food industries.

- Transgenic Animals. A transgenic animal is one that has had genetic material from another species inserted into its genome. The foreign DNA is then expressed by the animal; that is, the foreign DNA goes on to produce its product, usually a protein, in the body of the transgenic animal. These animals are unique models in which to study many genetic phenomena. An excellent example is the research on regulatory mechanisms called promoters. Promoters control gene expression; that is, they turn genes on and off. Scientists recently developed transgenic pigs that have the gene coding for a specific mouse milk protein and its promoter spliced into their DNA. The pigs later lactated varying levels of the mouse milk protein. Now transgenic cows and goats are being bred with the milk protein and promotor spliced into their DNA. If these large farm animals are able to express the mouse milk protein, they may be engineered in the future to express proteins with therapeutic value, thereby offering an efficient method of producing large quantities of drugs that are prohibitively expensive when manufactured by traditional techniques.

- Technique Spots Difficult to Detect Infections. Polymerase chain reaction (PCR) is a rapid and highly specific technique that allows scientists to amplify extremely small amounts of DNA or RNA for study of structure, function, or identification in situations where other systems are not sensitive enough to detect the desired sequence. Such quick identification of difficult to detect infections (that is, the DNA of the infectious agent) should lead to significantly improved treatments. For example, researchers using PCR have found the proportion of T-cells (immune system's lymphocytes) infected with HIV (the virus responsible for AIDS) to be 10 to 100 times higher than previously believed. This finding will have an impact on clinicians' ability to assess the relative merits of treatments for HIV infections. In another example, reliable detection of *Borrelia burgdorferi*, the tick-transmitted spirochete responsible for Lyme disease, has been difficult due to low levels of infectious agent in patients. Tests currently in use may miss as many as 10 percent of infected patients. Using PCR, it is possible to detect the one cell in a million that is infected.

- Adoptive Immunotherapy and Gene Transfer. For the first time, scientists have transferred cells containing foreign genes into a human patient. In order to monitor the results of an experimental cancer treatment, NIH scientists infused patients with tumor-infiltrating lymphocytes (TIL cells) that had been altered by the insertion of a marker gene so they could be tracked in the patient's body. After the TIL cells were reinfused, blood and tumor biopsies were taken at regular intervals to establish where the TILs went, how well they survived, and what they did. This procedure has proven to be both technically feasible and safe. A significant percentage of the transfected TIL cells localized to the tumor, although many remained in the blood stream. Future plans include insertion of genes for molecules, such as tumor necrosis factor and interleukin-2, to determine if they will enhance the tumor-killing potential of TIL cells.

- Organoids and Gene Transfer. NIH scientists have devised yet another method of transferring desirable genes and their products into mammalian bodies. In this case, an artificial organ called an organoid was implanted into the body of a rat. The organoid consists of rat liver cells growing on a pad of Goretex (nonwoven fibers of expanded polytetrafluoroethylene, the same type used to make plastic rain gear). The cells were encouraged to grow with a growth hormone and engineered to carry an altered bacterial gene, the viability of which could be detected by the researchers. The striking thing about these experiments is that the organoid was infiltrated by new blood vessels from the rat and was able to function for months like a viable body organ, secreting products into the blood stream via new vasculature. Moreover, the foreign gene remained functional in the cells. Even though all potential problems with the organoids have not yet been solved, studies like these make implantation of therapeutic genetic material into humans a possibility for the future.

- National Center for Biotechnology Information at NIH. In order to make the large and growing body of information generated by molecular biologists around the world useful for professionals in the biomedical community, a National Center for Biotechnology Information (NCBI) has been established at NIH, within the National Library of Medicine (NLM) in accordance with Public Law 100-607. Information access has become an urgent problem. For example, over 30 million base sequences (from the DNA of plants, animals, and man) have been reported thus far. Sequence information is of no use if it cannot be stored easily, accessed, and compared. The NCBI is beginning to integrate existing data bases and developing new computer programs to analyze them.

In a remarkably short period of time, the concepts and tools of molecular biology that are commonly referred to as biotechnology have diffused throughout virtually all of biomedical research. This is a very small selection from the myriad examples of advances made possible through application of biotechnology. Clearly, the future promises even more dramatic progress in disease treatment, diagnosis, and prevention.

NEUROBIOLOGY

Recombinant DNA technologies allow the dissection of the nervous system at a molecular level, while imaging devices scrutinize the working brain. These technologies offer endless opportunities to conduct innovative research on the diagnosis, treatment, and prevention of neurological disorders and renewed hope to those who suffer their devastations. Vigorous inquiry is taking place on virtually all neurobiological fronts; some recent scientific advances are discussed below.

- Arthritis Caused by Defective Brain Mechanism. Recent research has provided further understanding of the mechanisms involved in the development of human autoimmune diseases, especially rheumatoid arthritis. Two different strains of inbred rats were injected with bacterial cell fragments, triggering an immune response. The resulting inflammation induced one type of rat to develop arthritis; the other type was somehow resistant to the effects of the inflammation. However, when the resistant rats were given a drug that blocks the release of anti-inflammatory hormones (corticosteroids), they, too, became arthritic. This research demonstrates that a defect in the brain mechanism responsible for the release of corticosteroids could well be involved in the development of rheumatoid arthritis.

- Diagnostic Test for Alzheimer's Disease. Plaques containing amyloid beta-protein and nerve cell fragments found in the postmortem brains of Alzheimer's disease (AD) victims are among the major hallmarks of the disorder. The disease, therefore, is confirmed only upon death of the patient. However, amyloid beta-protein recently has been found outside the brain: in the skin, tissue just beneath the skin, intestines, and blood vessels of AD patients and in a small proportion of normal persons over age 77. This discovery may lead to the development of a practical diagnostic test for this disease which afflicts an estimated 2 million Americans. Such a test could also prove useful in monitoring the course of the disease and in judging the effectiveness of experimental treatments. These data suggest that AD may be a widespread systemic disorder and support other findings indicative of a metabolic defect. If so, it may be that the amyloid beta-protein is transported to the brain from elsewhere in the body. Blocking it from entering the brain might prevent or halt the progress of Alzheimer's disease.

- Spina Bifida. Malformations of the central nervous system are among the most devastating developmental defects in man; neural tube defects, such as spina bifida, are the most frequent and severe. NIH-funded research led to the development of the *curly tail* mouse mutant, which provides a particularly suitable model for the study of human spina bifida, since its deformity closely parallels the condition found in humans. The ability to manipulate the environment of the mouse embryos should provide important insights into the etiology of human spina bifida.

- Phenylketonuria (PKU) is a metabolic disorder responsible for a host of neurological impairments. Individuals with this abnormality may be born with a small head, become mentally retarded, have behavioral problems, and/or develop epilepsy. The affected individuals lack phenylalanine hydroxylase (PAH), a liver enzyme needed to metabolize phenylalanine, an amino acid essential for normal growth and development. The gene responsible for the production of PAH has been identified, mapped and cloned, allowing clinicians to diagnose PKU prenatally and to identify carriers of the defective gene in 90 percent of cases. Scientists using molecular genetic techniques have engineered the production of human PAH in mouse liver cells at a level comparable to that found in normal human liver. This development suggests that human gene therapy may be possible in the future.

- Hepatic Encephalopathy. Each year, over 30,000 Americans die of liver diseases because their physicians have difficulty treating them while they recover from hepatic encephalopathy, a neurological complication of liver failure characterized by mental confusion, even coma. Recently, NIH scientists discovered the process responsible for the syndrome--the accumulation of a naturally produced benzodiazepine-like sedative in the brain and peripheral tissues that depresses brain functions. These findings suggest that an effective means of reversing hepatic encephalopathy would be to treat patients recovering from liver failure with drugs that block molecular receptors to which the sedative must attach to be active. Nearly 80 percent of patients in European studies have thus far been successfully treated with such therapies.

- Nerve Growth Factor. One of the most interesting discoveries of basic neuroscience research is the fact that some brain cells continue to grow and change throughout the life span. This "neuronal plasticity" allows cells to establish new connections with other nerve cells and possibly compensate for those that die during the aging process. The ability of some nerve cells to grow and differentiate depends on the presence of nerve growth factor (NGF) in the brain. New studies suggest that NGF may promote neuron survival by acting upon gila, cells that help support nerve cells. NGF also is associated with non-neural tissues such as large blood vessels in the brain, which indicates that NGF may play an even larger role in normal nervous system functions. Further elucidation of the role of NGF is needed before clinical applications can be developed.

- Cell Replacement Therapy for Inherited Blinding Diseases. Two separate research teams, working independently, have successfully transplanted normal rat retinal pigment epithelium (RPE) cells into the eyes of rats with an inherited retinal degeneration. The RPE cell layer acts as an interface between the photoreceptor cells of the neuronal retina and its blood supply. When the RPE cells fail to perform their function, cellular debris accumulates, causing photoreceptor degeneration with resulting loss of vision. In the rat model used in these studies, transplantation of healthy RPE cells abruptly halted degeneration. This research advance raises the possibility of cell replacement therapy for inherited blinding diseases like retinitis pigmentosa.

While basic scientists continue to examine the intricate form and function of the nervous system, much of the knowledge gained from such exploration has immediate clinical application. In the case of HIV infection, basic knowledge helps clinicians deal with dementia in AIDS patients.

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

NIH continues to expand laboratory and clinical research aimed at preventing and treating human immunodeficiency virus (HIV) infection. Basic research in virology, molecular biology, and immunology has rapidly resulted in new information about the structure of the virus, its genetic variability, and the immune mechanisms triggered by infection. Clinical evaluations of vaccines, drugs, and therapies for AIDS-related infections and cancers have also proven valuable. For example, recently conducted clinical trials show that AZT delays onset of AIDS symptoms in those with early infections. The following descriptions highlight a few science advances in the field of AIDS research.

- Vaccine for AIDS-Like Disease. Scientists have developed a vaccine that appears to prevent AIDS-like disease in monkeys. The simian immunodeficiency virus (SIV) causes Simian AIDS (SAIDS) in macaque monkeys and is a close relative of HIV, the virus that causes AIDS in humans. Since there is a strong genetic and functional relationship between SIV and HIV and a physiological similarity between macaques and humans, the SIV/macaque disease model is highly relevant for AIDS research in humans. Aside from the vaccine development, studies of the SIV/macaque disease model have resulted in several contributions regarding the origins of HIV, AIDS pathogenesis, and drug research.

- Mouse Model of HIV Infection. Another good animal model of HIV infection has been developed recently. Homozygous severe combined immunodeficiency (SCID) mice are genetically immunodeficient due to a lack of functional T and B lymphocytes; that is, they are unable to mount an effective immune response to foreign antigens. However, when human lymphoid tissue containing functional lymphocytes is implanted in these mice, they develop a competent immune system. These mice then simulate the human immunological response to infection with HIV virus and may serve as a small animal model in which to study the interactions of HIV with the human lymphoid system.

- AIDS Dementia. The neurological effects of AIDS, particularly dementia, greatly add to personal suffering. Recent studies are attempting to reveal some of the dynamics involved. For example, patients with AIDS dementia have neurotoxic substances in their cerebrospinal fluid (CSF). Monoclonal antibodies to CD4, the cell receptor by which HIV gains entry to cells, are specifically effective in neutralizing the neurotoxic material present in the CSF of patients with AIDS dementia. These results improve understanding of AIDS dementia and also suggest possible therapeutic approaches to its amelioration. Another approach finds the level of glucose metabolism increasing greatly in areas of the brain infected by HIV; however, it declines as dementia progresses.

- Viral Enzymes Now Available for Research. In order to replicate itself, the AIDS virus must synthesize at least three enzymes. One of these is a protease required to process newly synthesized viral proteins. This enzyme has now been crystallized and examined by X-ray diffraction, which has permitted the construction of a model. This model shows in three-dimensions where each atom is located. Now it may be possible to synthesize compounds that inactivate this enzyme so critical to the growth of the AIDS virus, thereby opening a new front in the war against the AIDS epidemic.

- New Blood Screening Techniques. Promising new testing procedures have been developed to screen donated blood for HIV infection. In one such test, polystyrene beads are coated with HIV proteins capable of binding to HIV antibodies present in test specimen. A fluorescent-labeled immunoglobulin, which binds to the HIV-antibody complex, renders the antibodies detectable. This new test has proven more sensitive and specific than currently licensed HIV antibody tests. Another test using polymerase chain reaction (PCR) technology, described in the section on biotechnology, is capable of detecting one molecule of HIV DNA in 10 microliters of blood.

- Anti-AIDS Drugs. AZT is a widely used treatment for AIDS. However, its usefulness is limited by its toxic side effects, particularly that of bone marrow depression. Investigators have recently identified several related chemicals that may be as potent but less toxic than AZT. One of the most promising, dideoxyinosine (ddI), was developed at the National Cancer Institute (NCI). After obtaining a patent on the molecule and conducting a national competition among potential drug development collaborators, the NCI entered into an exchange licensing agreement with Bristol Myers, Inc. Preliminary results suggest that ddI, like AZT, causes a significant rise in the number of CD4 lymphocytes (a prognosticator of improving health) and a significant decline in antigen level (a high level is a marker of viral activity). AZT and ddI are soon to be compared in a large study designed to further investigate their comparative efficacy and long-term toxicity.

- Anti-AIDS Drugs and Children. The testing of anti-HIV drugs in children has very high priority because the number of pediatric HIV infections due to intravenous drug use in women of child-bearing age is rapidly increasing (a December, 1989 Center for Disease Control report states that there were 1,947 pediatric--under age 13--AIDS cases reported between December 1987 and November 1989.) A study evaluating continuous-infusion AZT in children with symptomatic HIV infection recently has been completed. The therapy was well-tolerated, and toxicity was mostly limited to bone marrow suppression. Dramatic improvement in IQs from baseline occurred in the small sample of children with significant brain dysfunction from HIV infection prior to treatment. Six children without detectable evidence of brain dysfunction prior to AZT also showed improvements in their IQs from baseline. These results suggest that cognitive impairment may be among the earliest manifestations of HIV infections in children. A Phase I study of ddI in children is nearly complete, and preliminary evidence shows that this agent has promising anti-HIV activity in children as well as in adults.

Even though anti-AIDS drugs like AZT and ddI promise prolonged life for AIDS patients, scientists will continue to search for improved treatments and ways to stop the action of the AIDS virus. Before any new treatments may be offered to the general public, however, these treatments must be tested for safety and efficacy in clinical trials.

CLINICAL TRIALS

A clinical trial is a method of determining prospectively the effect and value of medical interventions in human subjects and the side effects and complications resulting from their use over time. The knowledge resulting is directly applicable to man and, when applied, may enhance the quality of life, its duration, or both. Clinical trials provide the testing ground for potentially effective therapies prior to their initial, and later widespread clinical application, and thus allow for the orderly progression of research results from the fundamental level to the health care system. The following descriptions highlight recent clinical trials conducted or sponsored by the NIH, some of which are still in progress.

- New Drug Slows Progression of Parkinson's Disease. The preliminary results of a large, multicenter NIH-supported drug trial confirm previous findings that the drug *deprenyl* delays onset of the disabling Parkinson's disease symptoms requiring L-dopa therapy. These findings are the result of a 5-year clinical trial still in progress, which involves 800 Parkinson's patients at 28 medical centers in the United States and Canada. Parkinson's disease is characterized by tremors and lack of muscular control brought on by the inexplicable loss of nerve cells in the brain responsible for the production of dopamine, a neurotransmitter. Standard therapy has been to give Parkinson's patients L-dopa, a drug the body converts to dopamine. Since L-dopa's effects are short-lived and its prolonged use causes serious side effects, deprenyl's ability to delay the need for L-dopa is an important advance.

- Treatment Improves Survival of Patients with Dukes' C Colon Cancer. A new combination of drugs greatly improves the post-surgical survival prospects of patients with colon cancer that has progressed to Dukes' C stage--the point at which cancerous cells have spread to adjacent lymph nodes but not to distant parts of the body. Positive results noted in the experimental group during interim analysis of NIH-sponsored clinical trials prompted scientists to end the control arm of the trials. The trials were designed to judge the effectiveness of Levamisole, an intestinal parasite drug, in combination with 5-fluorouracil (5-FU), a standard anti-cancer drug. The drug combination, tested on 1,700 patients over the last 8 years, reduced the risk of recurrence and the mortality rate by one-third. Physicians, surgeons, and institutions across the country have been alerted to the potential benefits of this new therapy. At present, Levamisole can only be obtained by physicians and surgeons through the National Cancer Institute. Colon cancer strikes over 100,000 Americans each year; 21,000 are in stage C at the time of their diagnosis. More than half have been expected to die of the illness within 5 years, despite surgery.

- Detection and Treatment of Hepatitis C Viral Infection. Hepatitis C virus genes have been identified, allowing the synthetic production of one of its proteins and the detection of antibodies in infected individuals and in the Nation's blood supply. In addition, drug trials have confirmed the effectiveness of alpha interferon, a synthetically produced natural body protein, for the treatment of chronic hepatitis C viral infection. The Centers for Disease Control estimate that each year approximately 150,000 people develop hepatitis C, the most common form of hepatitis caused by blood transfusions. The hepatitis C virus is also transmitted intravenously during drug abuse and possibly by sexual contact. About 15 to 20 percent of people with chronic hepatitis C develop cirrhosis with permanent scarring and damage to the liver.

- Fiber and Colon Cancer. A 4-year randomized, double-blind, placebo-controlled trial was recently conducted to study the effects of dietary supplements on benign rectal polyps in patients with familial adenomatous polyposis. Familial adenomatous polyposis is an heritable disease in which benign rectal polyps are found in the colon and rectum; the condition usually becomes malignant before age 40. Fifty-eight patients who had their entire colons removed a year prior to entering the trial were given daily supplements of vitamin C (4 grams) and vitamin E (400 milligrams) alone or with 22.5 grams of grain fiber supplements. The results showed that, as the amount of ingested, prescribed fiber was increased, the number of rectal polyps decreased.

- Aspirin and Cardiovascular Disease. Results of *The Physicians' Health Study* suggests that 325 milligrams of aspirin taken every other day by men over 50 years of age reduces, by 44 percent, their risk of myocardial infarction, damage to heart tissue usually brought on by obstructed blood circulation to the heart. The study is a randomized, double-blind, placebo-controlled trial designed to study the cardiovascular benefits of low-dose aspirin in a group of 22,071 white, male physicians between the ages of 40 and 84. Because the cardiovascular mortality rate among the physicians in this trial was only 15 percent of that expected in a similar group in the general population, the evidence concerned with aspirin and prevention of total cardiovascular deaths remains inconclusive. There was a small increase in the number of strokes among those taking aspirin, but the difference from controls was not statistically significant. Because of the obvious benefit of the aspirin, that component of the study was terminated early, after an average 60.2 months. However, another component is still being tested--whether beta carotene reduces the incidence of cancer. Those results will be available in 1990.

This sampling of clinical trials addresses new treatments with great potential. The next section discusses vaccines, a form of prevention offering protection against infection. Vaccines also must be tested for safety and effectiveness in clinical trials.

VACCINE DEVELOPMENT

Vaccines are suspensions of weakened or killed microorganisms (whole or portions of bacteria, viruses, or rickettsiae) that, when injected into animals and humans, trigger an immune response that protects them from disease. An activated immune system produces proteins called antibodies that are precisely shaped to interact only with specific antigens, molecules intrinsic to the invading microorganism, e.g., toxins, proteins, polysaccharides. When the antigenic portion of a microorganism is engaged by an antibody, the microorganism often is rendered inactive and unable to threaten the individual.

- Better Vaccine for Pertussis (Whooping Cough). Whooping cough is a respiratory disease contracted by 60 million infants worldwide, resulting in 1 million deaths each year. These children could be protected by vaccination. The current pertussis vaccine (received in the DPT inoculation: diphtheria-pertussis-tetanus) is reasonably effective but associated with a relatively high incidence of side effects, some of which are serious. While the pertussis portion of the vaccine is made up of whole bacterial cells, investigators believe that antibodies that protect against whooping cough are produced in response to the organism's toxin, not the rest of the organism. To avoid side effects that may be triggered by those other portions, scientists have produced a vaccine consisting of an inactivated derivative of the toxin that still maintains its immunogenicity (ability to produce an immune response). The vaccine has been tested in adults, 18-month-old children, and infants 3 to 12 months, but further clinical trials will be necessary to be entirely certain of its safety and efficacy.

In another approach to improving the vaccine, investigators have identified mutants of the toxin protein that are potentially non-toxic or less toxic. This discovery raises the possibility of using proteins that do not require extensive detoxification, yet retain the antigenic capacity of the native protein. Other investigators have succeeded in engineering a cousin of the whooping cough bacteria to produce a non-toxic version of the pertussis toxin that is still capable of inducing immunity. The new toxin is currently under investigation to determine its immunogenicity, efficacy, and safety.

- The development of a Vaccine for Colon Cancer has yielded encouraging results. Patients who had their colon cancer surgically removed were assigned to receive either a vaccine made from their own tumor or no further treatment, as is standard practice. Four years of follow-up has revealed that the patients who received the vaccine had significantly fewer tumor recurrences and deaths than did those who received no postoperative therapy. The investigators were thus able to demonstrate a specific immune response in patients who were vaccinated; a large clinical trial is now under way.

- Conjugated Vaccines. The *Hemophilus influenzae* type b is a bacterium that causes meningitis and acquired mental retardation in children. NIH scientists pioneered the development of H. flu, a vaccine used world-wide against this microorganism. While very effective in children, the vaccine has not been effective in young infants due to the immaturity of their immune systems and its inadequate response to relatively weak antigens, such as those in H. flu. NIH scientists have now devised a new H. flu vaccine that confers protection from *Hemophilus influenzae* type b bacterium in children as young as 2 to 3 months. The new method binds (conjugates) the bacterium's antigen (a polysaccharide component of the capsule surrounding the microorganism) to a pertussis toxoid protein, thereby enhancing the antigen's ability to trigger an immune response.

The conjugating concept has also been applied when making vaccines against other bacteria that cause diseases of considerable public health significance, such as the salmonella bacterium (typhoid fever), pneumococcus (pneumonia), *Shigella dysentariae* (epidemic diarrhea), and *Staphylococcus aureus* (life-threatening bacteria found in burn patients, premature babies, and other hospitalized patients). A new vaccine also has been developed to decrease the impact of group B streptococcal (GBS) infection of newly born infants. The vaccine will be given to mothers known to be GBS positive in order to boost their antibody levels. Higher maternal antibodies levels will confer immunity on the fetus in utero, thereby protecting infants during their first 3 months of life, the period during which this devastating systemic infection is likely to occur.

- Vaccines of International Interest. NIH is involved in vaccine development and research elucidating basic immune response mechanisms in many diseases, some of which are diseases that affect populations other than our own. Examples include studies of malaria and denque, infectious diseases that occur in tropical regions and hepatocellular carcinoma, a disease caused by a hepatitis B virus infection early in life that is prevalent in many areas of the world, especially the Far East. Recently a vaccine capable of triggering an immune response against tuberculosis (TB) and leprosy has been developed using recombinant DNA technology. Each year 10 million new cases of TB occur globally, resulting in an estimated 3 million deaths. In the United States, approximately 22,000 new cases are reported; 2,000 victims die annually. As for leprosy, if clinical trials prove the vaccine safe and effective, it may affect the lives of 11 million people, primarily in Asia, Africa, and Latin America.

OTHER SELECTED ADVANCES

There are numerous scientific advances in many other areas of research, some of which are described below.

- DNA Greatly Magnified. Scientists have for the first time produced high resolution pictures of DNA using a technique called *scanning tunnelling microscopy (STM)*. STM can magnify objects up to a billion times their actual size. The new STM pictures verified what scientists in 1953 deduced about the structure of DNA using X-ray crystallography (a technique that bounces X-rays off crystals, thereby revealing the three-dimensional arrangement of their atoms), that it is a double helical structure. The new STM technique may in the future allow scientists to directly observe DNA interacting with other biological materials.

- Biological Mechanism that Control Cellular Iron Levels. Scientists at NIH have discovered a novel biological mechanism within the cell that controls iron levels. The mechanism involves a unique protein that responds to fluctuating cellular iron levels by changing its shape. When iron levels become too high, the protein becomes compact; when iron levels fall too low, the protein opens up. This changing architecture is facilitated by sulfur atoms within the protein that link up when iron levels are high and release each other when they are low. By changing its shape, the iron-sensing protein gives a signal to the cellular machinery responsible for making a protein that absorbs excess iron within the cell. Low iron levels lead to anemia. Too much iron is toxic, particularly in the liver. Understanding these mechanisms will eventually lead to better treatments. Since most proteins depend on sulfur to keep their shape, and since shape determines function, this body of research may also prove valuable in the study of other cellular mechanisms.

- Osteoporosis is a disease of major scientific and public health importance. The disorder is responsible for more than 1.3 million fractures of spine, hip, and wrist each year, at a total cost of between $7 and $10 billion annually. Researchers have demonstrated that decreased production of the active form of vitamin D is related to both osteoporosis and aging. Normally, it is produced in the kidney, subject to regulation by parathyroid hormone and phosphate levels. In osteoporosis, an abnormality in parathyroid hormone secretion has been uncovered, leading researchers to speculate that vitamin D or parathyroid hormone may prove effective in the treatment of osteoporosis.

Related research has recently demonstrated that thyroid hormone administration decreases bone density, possibly leading to osteoporosis. Since disorders requiring thyroid hormone treatment most often occur in women over the age of 40, and it is they who are at greatest risk of developing osteoporosis, careful administration of thyroid hormone is crucial. Highly sensitive assays that accurately determine when the necessary amount of hormone has been given have recently been developed.

- Soy Formula and Infant Development. Data collection has been completed in the congressionally mandated population-based study of children 9 to 10 years of age who were exposed to a chloride-deficient soy formula during infancy. The children were identified during a mail survey and were given a battery of psychological tests to determine if they had incurred any delay in intellectual development as a result of the exposure to the formula. A comparable group of age, sex, race, and socioeconomically matched children were used as controls. The data suggests that the children exposed to chloride-deficient formulas now appear to be performing at levels comparable to their peers, despite early delays in growth and development.

- Fish Protein and Incidence of Cardiovascular Disorders. The importance of a diet with adequate high-quality protein is important in the prevention of hypertension and stroke. In recent studies, investigators observed that blood pressure was higher and hemorrhagic stroke more frequent in rats on a low-protein diet. This same pattern has been noted for years in Japan, where stroke is most common in populations whose diet is lowest in protein. The investigators also found that increasing protein in the diet reversed the tendency toward hypertension and stroke. Only certain amino acids, however, were necessary to do so. These were the sulfur-containing amino acids, especially methionine and taurine, found mostly in animal protein and less commonly in vegetable protein. They are readily available in fish. Acute intravenous administration of sulfur-containing amino acids (amino-acids are the building blocks of proteins) acutely lowered blood pressure, and chronic administration in the diet reduced blood pressure, incidence of stroke, and signs of hypertension-induced damage in blood vessels, brain, and kidney. Sulfur-containing amino acids appear to affect the transport of calcium across cell membranes and thus the state of contraction of the smooth muscle cell that is the final cause of high blood pressure.

- Over-the-Counter Pain Medication and Chronic Kidney Disease. Scientists have correlated the prolonged use of analgesics containing phenacetin with chronic kidney disease. Most products containing the drug have been subsequently discontinued or reformulated. However, the compound acetaminophen, phenacetin's major metabolite, remains on the market. Acetaminophen is the active ingredient in numerous drugs, including some very common over-the-counter pain medications. A recent epidemiologic study demonstrated that the risk of chronic kidney disease is elevated for daily users of acetaminophen. Because so little is known about the causes of chronic kidney disease and because early detection is so difficult, no successful prevention programs have yet been implemented. If the overuse of this drug were stopped, at least 4 percent of chronic kidney disease might be prevented.

CONCLUSION

As this brief selection of science achievements illustrates, the National Institutes of Health continues to support research that investigates fundamental biomedical processes and those that apply knowledge generated from such investigations to the formulation of effective clinical interventions and disease preventions. Also evident in these achievements are the large number of studies that are being conducted at the molecular level. They are the direct result of recent advances in biotechnology, a discipline that will continue to expand the frontiers of biomedical science.

NATIONAL INSTITUTES OF HEALTH

Advisory and Assistance Services

Account Title and Symbol		FY 1989 Actual	FY 1990 Approp.	FY 1991 Estimate
I. Contractual Services				
Individual Experts and Consultants	B.A.	1,888,000	2,725,000	2,712,000
	Oblig.	1,888,000	2,725,000	2,712,000
	Outlays	1,909,000	2,569,000	2,648,000
Studies, Analyses & Evaluations	B.A.	2,295,000	2,129,000	1,150,000
	Oblig.	2,295,000	2,129,000	1,150,000
	Outlays	1,968,000	1,573,000	989,000
Management & Prof. Support Services 1/	B.A.	5,290,000	10,259,000	10,890,000
	Oblig.	5,290,000	10,259,000	10,890,000
	Outlays	4,380,000	7,816,000	9,221,000
Engineering & Technical Services	B.A.	2,000	10,000	15,000
	Oblig.	2,000	10,000	15,000
	Outlays	2,000	10,000	15,000
Subtotal	B.A.	9,475,000	15,123,000	14,767,000
	Oblig.	9,475,000	15,123,000	14,767,000
	Outlays	8,259,000	11,968,000	12,873,000
II. Personnel Appointments 2/	B.A.	501,000	886,000	908,000
	Oblig.	501,000	886,000	908,000
	Outlays	499,000	862,000	873,000
III. Advisory Committees	B.A.	0	0	0
	Oblig.	0	0	0
	Outlays	0	0	0
TOTAL	B.A.	9,976,000	16,009,000	15,675,000
	Oblig.	9,976,000	16,009,000	15,675,000
	Outlays	8,758,000	12,830,000	13,746,000

1/ Includes funds authorized by Section 2611 of the Public Health Service Act, providing that up to one percent of funds appropriated by the Public Health Service Act, the Community Mental Health Centers Act or P.L. 85-151 may be used for program evaluation. The evaluation estimates do not include the funds for the Office of the Assistant Secretary for Health or the Office of the Secretary.

2/ In accordance with instructions received from the Public Health Service, compensation for appointed advisory committee members is reflected in the Personnel Appointments category.

Description of the Need for Advisory and Assistance Services

The use of advisory and assistance services is of critical importance to the National Institutes of Health (NIH) in carrying out the mandates placed upon us by the Congress and the Administration.

The NIH is held accountable for continuing major new research initiatives of the highest national priority in such areas as Acquired Immune Deficiency Syndrome, Alzheimer's Disease, and genome mapping, in addition to continuing emphasis on prevention and sustaining a broadly based, balanced biomedical research enterprise. Reliance on a variety of advisory and assistance services mechanisms is absolutely essential to the effective development and monitoring of these crucial new programs as well as our existing programs. The areas of advisory and assistance services support are identified below:

Contractual Services: The NIH uses a number of contracts to provide management services and special studies. These contracts are necessary to NIH's research endeavors and it is impractical and uneconomical from a staff utilization point of view to perform these services in-house. Services and studies included in these categories are: a special project in Alzheimer Disease Education; support for the Women's Health Initiative and Minority Access to Research Careers programs; support for epidemiology studies; and software, programming, and technical assistance for NIH computer systems.

The NIH also contracts for specialized, ad hoc advisory support in scientific, medical, or technical areas not otherwise represented by NIH staff or the regularly appointed membership of NIH advisory groups. Procurement through contracts of this wide range of expert services required for the effective operation of the NIH is much more economical than maintaining a staff of such diverse talents. Individual experts and consultants may be scientists or non-scientists who bring knowledge of relevant programmatic areas of the Institutes. They possess familiarity with NIH procedures as well as awareness of the roles of the diverse institutions in biomedical research and the health needs of the American people, and are counted on in this regard to provide advice to senior program officials.

Program evaluation funds are included in this category to be used at the discretion of the Secretary, HHS, for the evaluation of health programs. Up to one half of the set-aside is made directly available to the individual agency to conduct studies. Each year at the direction of the Assistant Secretary for Planning and Evaluation, OS, and the Assistant Secretary for Health, PHS, a program of studies is planned and conducted by the Bureaus, Institutes, and Divisions of the NIH as well as by the Office of the Director, OD/NIH.

These evaluation studies aim to assist in program development and management decision making. Program evaluations involve examination of program structure, function, mechanisms, and output to determine how effectively the program mission is being accomplished and to what extent objectives are being realized through policies, procedures, and activities that have been established. Studies of agency-wide mechanisms of support, special areas of emphasis, and the development of evaluation methods and data bases are also essential features of the evaluation program.

The precise nature of the evaluation program emphasis in 1991 will be determined during the latter part of 1990. NIH will continue to support congressionally mandated studies, in addition to further development of evaluation methodology and cross-cutting studies of research support mechanisms and technology transfer programs.

Personnel Appointments: The planned appointments for 1991 will serve to provide specialized knowledge and expertise to advise, review, and evaluate the administration and management of the Institutes' programs, both intramural and extramural. This mechanism also provides scientific expertise in research areas that are planned for short-term study or that are concerned with infrequently occurring diseases or conditions. The appointed members of advisory committees are included in this category, and provide scientific, medical, and technical expertise to the NIH and perform services that are essential to the review process. These activities are integral to the effective planning and management of the NIH and bring a non-Federal perspective to the government-university-industry interaction.

Internal Controls: Policy guidelines exist in the form of OMB Circular A-120 and DHHS General Administration Manual 8-15. This guidance has been promulgated to make staff aware of the definition of Advisory and Assistance Services (AAS). Each year, a consultant services plan is prepared identifying planned AAS procurement in the next fiscal year. Several offices may be involved in determining the appropriate classification of an AAS project: the Bureau, Institute, Division (BID) Administrative and Executive Offices, as well as the BID Office of the Director, the appropriate procurement or contracting office and the NIH Division of Management Policy. At each level of review, the procurement is scrutinized to assure that the services are essential and cannot be provided by in-house personnel. All contracting regulations dealing with conflict-of-interest, a drug-free workplace, etc., apply to AAS awards. All procurement for AAS services are subject to approval by a designated approving official prior to award. The dollar amount of the procurement identifies the level of the approving official.

All small-purchase procurement are subject to audit by the NIH Division of Procurement. The Office of the Assistant Secretary for Health, PHS conducts periodic reviews of contracts awarded for AAS services.

NATIONAL INSTITUTES OF HEALTH

1991 CONGRESSIONAL JUSTIFICATION

Summary by Appropriation

(Dollars in thousands)
INCLUDES AIDS

	1989 Actual Budget Authority	1990 Estimate	1991 Estimate
NCI	$1,572,879	$1,634,294	$1,694,059
NHLBI	1,046,259	1,072,335	1,112,502
NIDR	131,026	135,744	140,520
NIDDK	559,886	581,466	605,349
NINDS	472,662	490,396	512,212
NIAID	743,870	832,960	886,875
NIGMS	683,920	712,030	745,494
NICHD	425,918	442,906	461,473
NEI	231,404	236,529	247,392
NIEHS	223,686	229,233	235,792
NIA	222,888	239,452	248,938
NIAMS	160,080	168,927	176,080
NIDCD	94,687	117,582	122,847
DRR	340,898	337,105	319,151
NCNR	29,195	33,513	35,127
NCHGR	28,230	59,538	108,029
FIC	14,164	15,656	16,355
Subtotal	6,981,652	7,339,666	7,668,195
NLM	77,883	85,728	89,916
OD	46,737	89,916	82,975
B&F	38,492	61,042	88,600
TOTAL, NIH	7,144,764	7,576,352	7,929,686
AIDS	(602,294)	(743,532)	(800,164)

Note--1990 and 1991 estimates exclude $200 in permanent budget authority expected to be derived from Cooperative Research and Development Agreements.

NATIONAL INSTITUTES OF HEALTH

1991 CONGRESSIONAL JUSTIFICATION

Summary by Appropriation

(Dollars in thousands)
EXCLUDES AIDS

	1989 Actual Budget Authority	1990 Estimate	1991 Estimate
NCI	$1,448,731	$1,483,990	$1,533,252
NHLBI	1,007,648	1,030,279	1,068,039
NIDR	126,885	131,082	135,518
NIDDK	556,210	576,146	599,558
NINDS	459,230	474,238	494,985
NIAID	430,982	439,002	463,468
NIGMS	673,019	697,416	730,007
NICHD	403,214	416,157	432,463
NEI	226,439	230,996	241,505
NIEHS	219,489	224,942	231,212
NIA	222,386	238,593	248,009
NIAMS	159,347	167,689	174,597
NIDCD	94,687	117,582	122,269
DRR	295,688	291,009	270,772
NCNR	28,434	32,526	33,979
NCHGR	28,230	59,538	108,029
FIC	9,510	10,758	11,148
Subtotal	6,390,129	6,621,943	6,898,810
NLM	77,804	85,235	89,384
OD	40,945	79,365	69,228
B&F	33,592	46,277	72,100
TOTAL, NIH	6,542,470	6,832,820	7,129,522

Note--1990 and 1991 estimates exclude $200 in permanent budget authority expected to be derived from Cooperative Research and Development Agreements.

NATIONAL INSTITUTES OF HEALTH

1991 CONGRESSIONAL JUSTIFICATION

Summary by Appropriation

(Dollars in thousands)
AIDS ONLY

	1989 Actual Budget Authority	1990 Estimate	1991 Estimate
NCI.................	$124,148	$150,304	$160,807
NHLBI...............	38,611	42,056	44,463
NIDR................	4,141	4,662	5,002
NIDDK...............	3,676	5,320	5,791
NINDS...............	13,432	16,158	17,227
NIAID...............	312,888	393,958	423,407
NIGMS...............	10,901	14,614	15,487
NICHD...............	22,704	26,749	29,010
NEI.................	4,965	5,533	5,887
NIEHS...............	4,197	4,291	4,580
NIA.................	502	859	929
NIAMS...............	733	1,238	1,483
NIDCD...............	---	---	578
DRR.................	45,210	46,096	48,379
NCNR................	761	987	1,148
FIC.................	4,654	4,898	5,207
Subtotal..........	591,523	717,723	769,385
NLM.................	79	493	532
OD..................	5,792	10,551	13,747
B&F.................	4,900	14,765	16,500
TOTAL, NIH........	602,294	743,532	800,164

DHHS - National Institutes of Health

1991 CONGRESSIONAL JUSTIFICATION

Summary by Mechanism

(Dollars in thousands)
INCLUDES AIDS

	1989 Actual Budget Authority		1990 Estimate		1991 Request	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	15299	$3,028,766	15683	$3,231,848	15344	$3,345,165
Admin. suppl	(438)	22,389	(469)	22,764	(434)	21,096
Competing	5382	982,491	4633	943,345	5095	1,058,514
Subtotal, RPGs	20681	4,033,646	20316	4,197,957	20439	4,424,775
Research Centers:						
Spec/comp	392	397,010	418	417,810	424	445,747
GCRC	78	107,474	78	115,284	78	116,082
Biotech	60	34,845	59	32,074	59	32,087
LASPR	51	48,611	53	50,433	53	51,043
RCMI	17	17,171	17	19,337	20	24,667
Subtotal, Centers	598	605,111	625	634,938	634	669,626
Other Research:						
Careers	1472	93,446	1539	104,856	1544	105,225
Clin. ed	44	2,983	29	2,942	29	2,942
Coop. cl	220	72,445	248	77,324	248	77,364
BRS	775	88,762	790	78,788	810	52,966
MBRS	98	37,826	98	39,622	98	43,045
Other	1259	75,571	1185	75,206	1192	76,167
Subtotal, Other Res	3868	371,033	3889	378,738	3921	357,709
Total, Res. Grants	25147	5,009,790	24830	5,211,633	24994	5,452,110
Training:						
Individual awards	1696	41,415	1944	50,542	1988	51,624
Institutional awards	9529	214,144	9851	236,120	10032	239,999
Total, Training	11225	255,559	11795	286,662	12020	291,623
R&D Contracts	1268	543,190	1345	576,495	1356	592,909
Intramural Research		788,810		855,947		914,913
RM&S		302,793		317,713		339,702
Control		74,100		74,944		75,459
Construction		7,410		16,272 1/		1,479
Total, IRDs		6,981,652		7,339,666		7,668,195
Nat'l Library of Med		77,883		85,728		89,916
Office of the Director		46,737		89,916		82,975
Buildings & Facilities		38,492		61,042		88,600
TOTAL, NIH		7,144,764		7,576,352		7,929,686
AIDS		(602,294)		(743,532)		(800,164)

1/ Includes $15,000 for Extramural Construction to be transferred to other accounts in accordance with Public Law 101-166.

Note--1990 and 1991 estimates exclude $200 in permanent budget authority expected to be derived from Cooperative Research and Development Agreements.

DHHS - National Institutes of Health

1991 CONGRESSIONAL JUSTIFICATION

Summary by Mechanism

(Dollars in thousands)
EXCLUDES AIDS

	1989 Actual Budget Authority		1990 Estimate		1991 Request	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	14908	$2,855,444	15188	$3,008,579	14731	$3,075,714
Admin. suppl	(428)	21,789	(467)	22,707	(432)	21,037
Competing	5127	925,648	4394	877,067	4856	1,011,946
Subtotal, RPGs	20035	3,802,881	19582	3,908,353	19587	4,108,697
Research Centers:						
Spec/comp	381	381,765	406	402,367	412	430,158
GCRC	78	89,802	78	92,651	78	92,651
Biotech	60	34,503	59	31,706	59	31,706
LASPR	40	32,854	42	33,175	42	33,175
RCMI	17	13,842	17	15,965	20	20,595
Subtotal, Centers	576	552,766	602	575,864	611	608,285
Other Research:						
Careers	1457	92,494	1,522	103,688	1,528	104,137
Clin. ed	44	2,983	29	2,942	29	2,942
Coop. cl	217	68,995	245	73,527	245	73,527
BRS	775	87,080	790	78,023	810	52,174
MBRS	98	37,592	98	39,432	98	42,785
Other	1223	66,694	1153	67,555	1,161	68,317
Subtotal, Other Res	3814	355,838	3837	365,167	3871	343,882
Total, Res. Grants	24425	4,711,485	24021	4,849,384	24069	5,060,864
Training:						
Individual awards	1624	39,649	1,872	48,609	1,916	49,659
Institutional awards	9305	209,377	9,618	230,736	9,799	234,461
Total, Training	10929	249,026	11490	279,345	11715	284,120
R&D Contracts	1021	376,447	1,060	377,858	1,064	384,915
Intramural Research		695,422		733,489		780,021
RM&S		281,179		291,526		311,952
Control		74,100		74,944		75,459
Construction		2,470		15,397 1/		1,479
Total, IRDs		6,390,129		6,621,943		6,898,810
Nat'l Library of Med		77,804		85,235		89,384
Office of the Director		40,945		79,365		69,228
Buildings & Facilities		33,592		46,277		72,100
TOTAL, NIH		6,542,470		6,832,820		7,129,522

1/ Includes $15,000 for Extramural Construction to be transferred to other accounts in accordance with Public Law 101-166.

Note--1990 and 1991 estimates exclude $200 in permanent budget authority expected to be derived from Cooperative Research and Development Agreements.

DHHS - National Institutes of Health

1991 CONGRESSIONAL JUSTIFICATION

Summary by Mechanism

(Dollars in thousands)
AIDS ONLY

	1989 Actual Budget Authority		1990 Estimate		1991 Request	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	391	$173,322	495	$223,269	613	$269,451
Admin. suppl	(10)	600	(2)	57	(2)	59
Competing	255	56,843	239	66,278	239	46,568
Subtotal, RPGs	646	230,765	734	289,604	852	316,078
Research Centers:						
Spec/comp	11	15,245	12	15,443	12	15,589
GCRC	0	17,672	0	22,633	0	23,431
Biotech	0	342	0	368	0	381
LASPR	11	15,757	11	17,258	11	17,868
RCMI	0	3,329	0	3,372	0	4,072
Subtotal, Centers	22	52,345	23	59,074	23	61,341
Other Research:						
Careers	15	952	17	1,168	16	1,088
Clin. ed	0	0	0	0	0	0
Coop. cl	3	3,450	3	3,797	3	3,837
BRS	0	1,682	0	765	0	792
MBRS	0	234	0	190	0	260
Other	36	8,877	32	7,651	31	7,850
Subtotal, Other Res	54	15,195	52	13,571	50	13,827
Total, Res. Grants	722	298,305	809	362,249	925	391,246
Training:						
Individual awards	72	1,766	72	1,933	72	1,965
Institutional awards	224	4,767	233	5,384	233	5,538
Total, Training	296	6,533	305	7,317	305	7,503
R&D Contracts	247	166,743	285	198,637	292	207,994
Intramural Research		93,388		122,453		134,892
RM&S		21,614		26,187		27,750
Control		0		0		0
Construction		4,940		875		0
Total, IRDs		591,523		717,723		769,385
Nat'l Library of Med		79		493		532
Office of the Director		5,792		10,551		13,747
Buildings & Facilities		4,900		14,765		16,500
TOTAL, NIH		602,294		743,532		800,164

NATIONAL INSTITUTES OF HEALTH

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1980...............	$3,185,928,000	$3,381,030,000	$3,367,757,000	$3,428,935,000 2/
1981...............	3,512,320,000	3,572,427,000	3,564,765,000	3,569,406,000 3/
1982...............	3,310,985,000 4/	3,834,958,000	3,818,710,000	3,641,875,000 5/
1983...............	3,748,771,000	4,013,450,000	4,028,591,000	4,023,969,000 6/
1984...............	4,091,958,000	4,314,501,000 7/	4,322,912,000 7/	4,493,588,000 8/
1985...............	4,566,453,000	4,834,343,000 9/	5,170,203,000	5,149,459,000
1986...............	4,852,680,000	5,247,836,000	5,463,658,000	5,498,454,000
1986 Sequester.....				-236,243,000
1987............ 11/	4,936,157,000	6,152,775,000	6,080,875,000	6,182,910,000
1988...............	8,260,277,000	7,036,285,000 12/	6,408,176,000	6,666,693,000
1989...............	6,535,207,000 13/	6,862,495,000 14/	7,199,298,000	7,152,207,000
1990...............	6,776,727,000 15/	7,678,625,000 16/	7,713,064,000 16/	7,672,922,000 17/
1990 Sequester.....				-96,570,000
1991...............	7,929,686,000			

1/ Reflects enacted supplementals, rescissions and reappropriations.

2/ Authority was a Continuing Resolution; reflects a rescission of -$446,000,000 authorized under P.L. 96-304.

3/ Authority was a Continuing Resolution; reflects a rescission of -$47,041,000 authorized under P.L. 97-12.

4/ September budget, original request was $3,762,483,000.

5/ The 1982 Continuing Resolution was the lower of the House or Senate less a four percent reduction.

6/ Authority was a Continuing Resolution.

7/ Excludes $166,368,000 not considered.

8/ Includes $175,838,000 authorized under a Continuing Resolution.

9/ Includes $237,435,000 not considered.

10/ Excludes $217,943,000 not considered.

11/ The budget estimate to Congress proposed that all funding for AIDS ($198,943,000) research be consolidated in the Office of the Assistant Secretary for Health. The House allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate allowance and the appropriation spread the funding among the institutes.

12/ The House allowance consolidated all NIH AIDS funding ($472,428,000) in the Office of the Assistant Secretary for Health.

13/ The 1989 request excludes funds for AIDS research and education ($587,630,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

14/ Excludes $249,464,000 not considered.

15/ The 1990 request excludes funds for the National HIV program ($752,670,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

16/ Includes $752,670,000 for AIDS Research.

17/ Reflects reductions of $10,000,000 for extramural salary cap savings, $4,000,000 for procurement reform and a $10,428,000 reduction in salaries and expense. Includes $743,542,000 for AIDS Research.

TUESDAY, MARCH 13, 1990.

NATIONAL CANCER INSTITUTE

WITNESSES

DR. SAMUEL BRODER, DIRECTOR, NCI

DR. MARYANN ROPER, DEPUTY DIRECTOR, NCI

DR. WILLIAM F. RAUB, ACTING DIRECTOR, NIH

PHILIP D. AMORUSO, ASSOCIATE DIRECTOR FOR ADMINISTRATIVE MANAGEMENT, NCI

JOHN P. HARTINGER, FINANCIAL MANAGER, NCI

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. NATCHER. At this time, we take up the budget request for the fiscal year 1991 for the National Cancer Institute, and we have before the committee Dr. Samuel Broder, the Director.

And Doctor, before we take up the request for the National Cancer Institute, tell us who you have with you there at the table.

Dr. BRODER. Thank you very much, Mr. Chairman.

I would like to introduce the people at the table. On my right is Dr. Maryann Roper, who is the Deputy Director of the National Cancer Institute. Perhaps I could take this opportunity to say that it's with great regret that I announce to the committee that Dr. Roper will be leaving. She's going with her husband, Dr. Bill Roper, to Atlanta.

Dr. Bill Roper was recently appointed to be the head of the CDC, and we will very much miss Maryann.

To her right is Dr. Bill Raub, who is the Acting Director of NIH; and further to the right is Mr. Dennis Williams, who is the Deputy Assistant Secretary for Budget, DHHS. On my left is Mr. Phil Amoruso, the Associate Director for Administrative Management, NCI and Mr. John Hartinger, the Financial Manager, NCI.

Mr. NATCHER. Thank you, Dr. Broder.

Dr. Broder, on behalf of our Subcommittee also the full Committee on Appropriations, I want to thank you and all of you ladies and gentlemen that are here today from the National Cancer Institute for the assistance you give us down through the years in regard to matters concerning members of Congress who have problems with cancer either themselves or with members of their family.

You have been of great assistance to a number of these Members and their families, and we appreciate it. We want you to know it.

It has been of great concern to us about several of these cases, and we appreciate the assistance that you have given us.

So now, Dr. Broder, I want to ask you the same question that I used to ask Dr. DeVita each year, and Dr. DeVita is an able man. I think all of you ladies and gentlemen would agree with that.

When he would come in, I would say to him, Dr. DeVita, what can you tell us this year that you didn't tell us last year? I am not going to ask you that, Dr. Broder. I am going to ask you to give us your statement and tell us what you are doing now, and we will be glad to hear from you.

Dr. **Broder**. Sir, with your permission, I would like to read a statement and also submit one for the record. I will try to be brief.

I would like to thank the distinguished chairman and the distinguished members of this committee for the opportunity to be here.

One million Americans will learn this year that they have cancer and about half of them will eventually die of this disease. Our best response to the challenge of cancer—a disease which causes suffering beyond metaphor—must be an intense effort to generate knowledge and to apply it quickly.

FOUNDATION STONES OF NCI

To do this, we rely on the three foundation stones of the NCI: basic research, clinical trials in prevention and therapy, and the cancer centers. Each plays a crucial part.

There is another overriding principle: the results of NCI's research belong to all Americans regardless of their race, age, income, social status, or place of residence.

I am sure you are aware that cancer research and technology transfer require creative, highly-trained scientists and clinicians and well-equipped laboratories.

Other resources are needed, such as a network of cancer centers, each bringing interdisciplinary approaches to cancer in its community, as well as addressing national and regional problems. An array of organized clinical trials is needed to generate knowledge regarding new drugs, preventions, and therapies. A vigorous program of clinical trials must involve academic centers and community physicians.

Science and the scientific method must underlie every activity of the NCI. In this regard, this has been a year of high achievement at the National Cancer Institute.

RECENT ACCOMPLISHMENTS

I would like to cite a few recent research accomplishments. For instance, two NCI scientists together with a colleague from the National Heart, Lung, and Blood Institute made medical history last spring by inserting new genetic materials into human cells, returning the cells back to the patient, and then tracking the gene-engineered cells in the patient's circulatory system two months later. These experiments have led us to the threshold of gene therapies and are based upon NCI basic research accomplishments.

NCI-supported clinical trials continue to make gains in some cancers using adjuvant treatment after surgery that can reach remaining microscopic tumors, prevent tumor recurrence, and prolong or save lives. For example, last year adjuvant treatment using a combination of levamisole and 5-fluorouracil, after surgery in Dukes' C colon cancer, an advanced cancer, made an improvement in the five-year survival rate, reducing deaths by a third. There will be approximately 110,000 new cases of colon cancer in 1990, of which 21,000 will be classed as Dukes' C stage.

Since last May, when this treatment became available under the Group C mechanism—which means that the NCI distributes the drug to doctors free of charge—the number of patients receiving it jumped from 10 a week to 200—now about 40 percent of eligible patients are receiving the treatment.

Neoadjuvant therapy, that is using chemotherapy or radiotherapy before surgery, may shrink certain cancers and make it possible to limit surgery, permitting the salvage of structures like the bladder, rectum or breast which would otherwise have been sacrificed to stop the cancer.

Especially impressive gains have been made in esophageal cancer, a highly lethal tumor that has been difficult to treat with surgery. Now, chemotherapy using cis-platinum in combination with other drugs and coupled with radiation before surgery can provide striking responses in some patients.

CANCER PREVENTION

NCI has a long commitment to cancer prevention. Chemoprevention studies are being carried out in breast, lung, colon, bladder, and skin cancers with agents related to the retinoids, beta-carotene, vitamin E, selenium, and other substances. A recent study showed that high wheat fiber diet decreased the number of large bowel polyps—cancer precursors. This study was conducted in patients at high risk for large bowel cancer, but this diet may reduce the risk of bowel cancer among all Americans.

At the same time as we are pursuing more prevention strategies, NCI is studying interventions with people already at high risk. One study is testing the effect of beta-carotene and retinol for asbestos workers and heavy smokers with the goal of decreasing lung cancer. Over 17,000 participants will be given either beta-carotene and retinol or a placebo. They will be recruited over five years and then followed an additional three years—so some will be studied for eight years. Five cities are participating: Baltimore, New Haven, Portland, San Francisco, and Seattle.

Another study is evaluating the effect of adding wheat bran fiber combined with calcium to the diet of individuals who have had a benign but premalignant polyp removed and are considered at high risk of colon cancer. A controlled study will compare polyp development in those who have the supplement and those who do not.

In another strategy aimed at cancer prevention, NCI conducts national programs to educate the public about cancer, at times using innovative approaches such as working with a major supermarket chain located in minority neighborhoods to highlight food choices that may help to reduce the risk of cancer. The innercity program is based on the four-year NCI/Giant Food "Eat for Health" program. It is reasoned that since people shop several times a week that this is a good way to reach under-served people with nutrition messages.

Reaching out to all Americans, NCI makes state-of-the-art information available to everyone in the country through the Cancer Information Service (CIS) via its toll free 1-800-4-CANCER number.

Over 500,000 people called CIS last year. Counselors use NCI's computerized Physician Data Query (PDQ) which describes state-of-the-art cancer treatment and available clinical trials. Today's CIS is now reaching more states and more people than ever before. And last year, NCI mailed out about 20 million brochures and pamphlets.

CANCER INCIDENCE AND MORTALITY

There is good news and bad news in our cancer incidence and mortality statistics. For Americans under 65, the death rate for certain cancers is clearly falling. Nevertheless, since 1973 the overall incidence of cancer has risen 14.6 percent and the mortality rate has risen 5.4 percent. And again this year, NCI statistics show that minority groups, the poor, the under-served and those over 65 have disproportionately high rates of cancer. The reasons are complex and relate in part to special problems in terms of access to state-of-the-art prevention, early detection, and treatment.

In response, NCI has made reduction of cancer mortality in these populations a high priority.

We must come to terms with these cancer statistics. Thus, we cannot allow the good news to induce us to overlook the bad news. But at the same time, we should not allow the bad news to eclipse legitimate areas of progress.

To guide epidemiologic studies and programs aimed at reduction of cancer in under-served groups, NCI is publishing a new atlas of cancer mortality in nonwhite populations which shows geographic areas with high rates of cancer.

Also to this end, NCI has incorporated the National Black Leadership Initiative on Cancer which assists black community-based and national leaders in organizing programs for early detection and prevention of cancer.

BREAST AND CERVICAL SCREENING

What more can be done? Early detection of cancer saves lives and is not used to full advantage. The Pap test is widely available, yet 6,000 women die each year of cervical cancer. NCI has improved screening for cervical cancer and is working to increase its use. Breast cancer is one of the leading causes of cancer death in women with roughly 150,000 new cases and 44,000 deaths in the United States expected in 1990, deaths that could be reduced by 30 percent or more if mammography guidelines were followed.

Last fall, a Women's Leadership Summit on Mammography was held on Capitol Hill to launch NCI's National Breast Screening Awareness Campaign in an effort to reduce breast cancer deaths by expanding mammography utilization. The Summit assembled hundreds of women from all across the country and organized them to return to their home regions and mobilize efforts to increase the use of mammography.

TREATMENT ADVANCES

Nor do we ignore today's patients. NCI's treatment research brings hope to those who are suffering today. New treatments are developed through clinical trials, and where early results are promising, special interim Food and Drug Administration classifications such as the Group C mechanism allow private physicians to use the drug for appropriate patients. This is extremely important because for some cancers experimental drugs are the only effective treatment available.

The following drugs were placed in Group C status last year: levamisole plus 5-fluorouracil for adjuvant treatment of Dukes' C colon cancers; deoxycoformycin for the treatment of hairy cell leukemia refractory to the standard treatment of alpha interferon; and fludarabine phosphate for refractory chronic lymphocytic leukemia which represents a significant advance in this common kind of leukemia in adults, with about 9,600 new cases each year.

Compounds developed at NCI and recently given new drug approval (prescription) status include: ifosfamide, flutamide, and carboplatin for treatment of the metastatic stage of testicular, prostatic, and ovarian cancer respectively.

NCI's research is helping to prolong survival by improving management of drug resistance which can render certain cancers impervious to chemotherapy. Researchers have found that adding the drug verapamil, a calcium channel blocker used in cardiology, to the usual chemotherapy regimen reduced drug resistance in patients with refractory myeloma and non-Hodgkin's lymphoma.

An old drug, Suramin, long used for treating parasitic infections, is the first new drug to have been found active in treating advanced prostate cancer. Currently, clinical trials using Suramin to treat prostate cancer are taking place at several medical centers.

All of us are aware of the challenge and difficulties that we face. Progress against the suffering and deaths from cancer will not be easy, but we have built a program where success is occurring in several important areas and the support evidenced by the President's budget ensures that it will continue to occur.

Mr. Chairman, the 1991 budget request for the NCI totals $1,694,059,000. I would be pleased to answer any questions.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Cancer Institute

One million Americans will learn this year that they have cancer and about half of them will eventually die of cancer. Our best response to the challenge of cancer -- a disease which causes suffering beyond metaphor -- must be an intense effort to generate knowledge and to apply it quickly. The three foundation stones of the NCI are: basic research, clinical trials in prevention and therapy, and the cancer centers. The results of NCI's research belong to all Americans regardless of their race, age, income, social status, or place of residence.

Cancer research and technology transfer require creative, highly-trained scientists and clinicians and well equipped laboratories. Other resources are needed, such as a network of cancer centers, each bringing interdisciplinary approaches to cancer in its community, as well as addressing national and regional problems. An array of organized clinical trials is needed to generate knowledge regarding new drugs, preventions, and therapies. A vigorous program of clinical trials must involve academic centers and community physicians.

Among other achievements, two NCI scientists (together with a colleague from the National Heart, Lung, and Blood Institute) made medical history last Spring by inserting new genetic material into human cells, returning the cells back to the patient, and then tracking the gene-engineered cells in the patient's circulatory system two months later. These experiments will lead to gene therapies and are based upon NCI basic research accomplishments.

Recently, NCI-supported scientists have made a number of important molecular discoveries, including: the location of molecular abnormalities believed to contribute to lung, colon and breast cancer by a loss of a critical regulatory mechanism; the location of the gene responsible for familial malignant melanoma; and the identification of five proteins implicated in the process of metastasis (the wild spread of cancer). Such discoveries pave the way for future research on prevention and cure of cancer.

For over 50 years, scientists have sought the cause of cystic fibrosis, and recently NCI-supported scientists discovered that the cystic fibrosis gene was linked to an oncogene (called met) thus providing a marker, which greatly facilitated the recent discovery and cloning of the cystic fibrosis gene.

NCI-supported clinical trials have shown that in some cancers, adjuvant treatment after surgery can reach remaining microscopic tumors, prevent tumor recurrence, and prolong or save lives. Last year adjuvant treatment using a combination of levamisole and 5-Fluorouracil, after surgery in Dukes' C colon cancer, an advanced cancer, made an improvement in five-year survival rate, reducing deaths by a third. There will be approximately 110,000 new cases of colon cancer in 1990, of which 21,000 will be classed as Dukes' C stage.

Neoadjuvant therapy, that is using chemotherapy or radiotherapy before surgery, may shrink certain cancers and make it possible to limit surgery, permitting the salvage of structures like the bladder, rectum or breast which would otherwise have been sacrificed to stop the cancer.

Clinical trials often take years to complete. Now, in addition to large clinical cooperative groups, NCI is using the mass media to draw attention to clinical trials. Accelerated enrollment speeds evaluation of new therapies and brings state-of-the-art therapies to more people.

NCI has a long commitment to cancer prevention. Chemoprevention studies are being carried out in breast, lung, colon, bladder, and skin cancers with agents related to the retinoids, beta-carotene, vitamin E, selenium, and other substances. A recent study showed that a high wheat fiber diet decreased the number of large bowel polyps -- cancer precursors. This study was conducted in patients at high risk for large bowel cancer, but this diet may reduce the risk of bowel cancer among all Americans.

Sometimes research affects us right in our own backyards; NCI-supported scientists have studied and identified the mutagenic substances formed when meat is grilled or fried. These substances may contribute to a risk for certain cancers and a better understanding of this process should help to lessen this risk.

NCI is studying interventions with people already at high risk. One study is testing the effect of beta-carotene and retinol for asbestos workers who are at high risk for lung cancer. Another study is evaluating the effect of dietary fiber combined with calcium in individuals who have a high risk of colon cancer.

NCI conducts national programs to educate the public about cancer, at times using innovative approaches such as working with supermarkets in minority neighborhoods to highlight food choices that may help to reduce the risk of cancer.

NCI makes state-of-the-art information available to everyone in the country through the Cancer Information Service (CIS) via its toll-free 1-800-4-CANCER number. Over 500,000 people called CIS last year. Counselors use NCI's computerized Physician Data Query (PDQ), which describes state-of-the-art cancer treatment and available clinical trials. This CIS is now reaching more states and more people than ever before.

For white Americans under 65 the death rate for certain cancers is falling. But again this year, NCI statistics show that minority groups, the poor, the underserved and those over 65, have disproportionately high rates of cancer mortality. The reasons are complex and relate in part to special problems in terms of access to state-of-the-art prevention, early detection, and treatment. In response, NCI has made reduction of cancer mortality in these populations a high priority.

NCI is publishing a new atlas of cancer mortality in nonwhite populations which shows geographic areas with high rates of cancer and this will guide epidemiologic studies and programs aimed at reduction of cancer in underserved groups. Also to this end, NCI has incorporated the National Black Leadership Initiative on Cancer which assists black community-based and national leaders in organizing programs for early detection and prevention of cancer.

Lifestyle changes, compliance with screening guidelines and smoking cessation, can prevent cancer deaths. Consequently, lung cancer deaths for men in some age groups are declining -- slowly, but surely. Lung cancer accounts for 30 percent of cancer deaths, so any reductions will make a marked impact on cancer mortality in the future. Unfortunately, we need to do more to reach women and adolescents.

Early detection of cancer saves lives and is not used to full advantage. The Pap test is widely available, yet 6,000 women die each year of cervical cancer. NCI has improved screening for cervical cancer and is working to increase its use. Breast cancer is one of the leading causes of cancer death in women with 150,000 new cases and 44,000 deaths in the United States expected in 1990 -- deaths that could be reduced by 30 percent or more if mammography guidelines were followed.

Last Fall, a Women's Leadership Summit on Mammography was held on Capitol Hill to launch NCI's National Breast Screening Awareness Campaign in an effort to reduce breast cancer deaths, by expanding mammography utilization.

Where early detection or state-of-the-art treatment programs have been established, beneficial results are seen. A report from the San Francisco/ Oakland based Surveillance Epidemiology and End Result Program shows striking changes in early breast cancer detection and a dramatic shift towards less radical surgical treatment.

Treatment research brings hope to today's cancer patient. New treatments are developed through clinical trials and where early results are promising, special interim Food and Drug Administration classifications, such as the Group C mechanism, allow private physicians to use the drugs for appropriate patients. This is extremely important because for some cancers experimental drugs are the only effective treatment available. The following drugs were placed in Group C status last year: levamisole plus 5-fluorouracil for adjuvant treatment of Dukes' C colon cancers; deoxycoformycin for the treatment of hairy cell leukemia refractory to the standard treatment of alpha interferon; and fludarabine phosphate for refractory chronic lymphocytic leukemia which represents a significant advance in this common kind of leukemia in adults, with about 9,600 new cases each year.

Compounds developed at NCI and recently given New Drug Approval (prescription) status include: ifosfamide, flutamide, and carboplatin for treatment of the metastatic stage of testicular, prostatic, and ovarian cancer respectively. A New Drug Approval application for fludarabine for chronic lymphocytic leukemia has been made.

NCI's research is helping to prolong survival by improving management of drug resistance which can render certain cancers impervious to chemotherapy. Agents being studied to combat drug resistance include: steroids and steroid antagonists, calcium channel blockers, cardiac antiarrhythmic drugs, immunosuppressants and monoclonal antibodies. Researchers have found that adding the drug verapamil, a calcium channel blocker used in cardiology, to the usual chemotherapy regimen reduced drug resistance in patients with refractory myeloma and non-Hodgkin's lymphoma.

An old drug, suramin, long used for treating parasitic infections, is the first drug to have been found active in treating advanced prostate cancer, which has failed conventional therapies.

Clinical trials on breast cancer are comparing the effectiveness of tamoxifen, with and without radiation therapy, in women whose cancer has not spread to nearby underarm lymph nodes. Over 2,600 women will participate, but nearly 70,000 women have similar cancers.

A study on small cell lung cancer is comparing standard treatment (chemotherapy and a daily dose of radiation) with an experimental regimen which uses the same chemotherapy, but with smaller, more frequent doses of radiation. About 360 people will be enrolled in this study over two years, but approximately 80,000 Americans would qualify by these criteria.

A number of clinical trials are testing natural human biological substances as novel treatments. Colony stimulating factors (CSF) which originate in the bone marrow, are proving useful in some hard-to-treat childhood cancers, such as neuroblastoma and aggressive lymphoma. These factors are improving statistics for treating other cancers, e.g., breast cancer. The CSFs appear to protect the bone marrow (the site of production of blood components) during high-intensity chemotherapy.

Although not the lead NIH agency, NCI has an important role in AIDS drug and vaccine development and NCI scientists continue to investigate the pathogenesis of AIDS, the biologic mechanisms by which the HIV causes infection, immune system destruction, multi-organ system dysfunction and some specific HIV-related cancers. The NCI intramural program has emerged as one of the most important centers in the world for development of therapeutics for children with AIDS.

Last year, 16 new anti-viral drugs have moved into preclinical testing. Compounds are evaluated for activity against HIV on a high-capacity screen of cells. Since 1987, over 14,000 chemical structures have been tested, of which 70 had anti-HIV activity. It is expected that up to 100 anti-HIV compounds may be identified each year -- with only three to four compounds developed each year.

In addition, NCI continues several AIDS epidemiologic and natural history studies, both descriptive and interventional, in the United States and abroad.

This research has had encouraging results. An individual diagnosed with AIDS in 1982 had only a 30 percent chance of being alive 18 months after diagnosis. This situation improved first at the end of 1986 and then dramatically in 1987. AZT, a drug developed by NCI in collaboration with a private sector company, was approved by the FDA in March of 1987. Thus, an individual diagnosed in 1987 had a greater than 60 percent chance of being alive at 18 months.

All of us are aware of the challenge and difficulties that we face. Progress against the suffering and deaths from cancer will not be easy, but we have built a program where success is possible and the continued support evidenced by the President's Budget ensures that it will occur. Mr. Chairman, the 1991 budget request for the NCI totals $1,694,059,000. I would be pleased to answer any questions.

CURRICULUM VITAE
SAMUEL BRODER, M.D.

EDUCATION:	1966	B.S. - University of Michigan, College of Literature, Science and the Arts, Ann Arbor, MI (high honors)
	1970	M.D. - University of Michigan, Ann Arbor, MI (cum laude)

EMPLOYMENT:

1970-1971	Internship (Medicine), Stanford University, Palo Alto, CA
1971-1972	Residency (Medicine), Stanford University, Palo Alto, CA
1972-1975	Clinical Associate, Metabolism Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD
1975-1976	Investigator, Medicine Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD
1976-1981	Senior Investigator, Metabolism Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD
1981-1988	Associate Director, Clinical Oncology Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, MD
1989-pres	Director, National Cancer Institute, National Institutes of Health, Bethesda, MD

HONORS, SOCIETIES and ORGANIZATIONS:

Phi Beta Kappa
Alpha Omega Alpha
Fellow of the Life Insurance Medical Research Fund
Upjohn Achievement Award
Arthur S. Flemming Award
Public Health Service/Meritorious Service Medal
Public Health Service/Distinguished Service Medal
Thirty-seventh Augustus B. Wadsworth Lectureship
Third Mullin Lectureship/University of Scranton
Fourth Biennial Chemistry as a Life Science Lectureship/Rutgers University
Twelfth Annual CIBA-GEIGY DREW Award in Biomedical Research
Alpha Omega Alpha Distinguished Professor, Dartmouth Medical School
Robert T. Wong, M.D. Endowment Award, University of Hawaii Foundation
Samuel Rudin Award, Columbia Presbyterian Hospital
First Annual Institute of International Health & Development Award
Gilman Honors Award/New York University
Harvey W. Wiley Medal/FDA Commissioner's Special Citation
American Society for Clinical Investigation (elected 1980)
Association of American Physicians (elected 1989)

American Federation for Clinical Research (Eastern Section Councilor)
American Association for Cancer Research
American Society for Clinical Oncology
American Association of Immunologists
Clinical Immunology Society
Editorial Advisory Board for numerous journals
Editor, Symposium on HTLV, September 1985, Cancer Research
Editor, AIDS: Modern Concepts and Therapeutic Challenges
Fellow, American College of Physicians

BOARD CERTIFICATIONS and LICENSES:

1973	Certified in Internal Medicine
1977	Certified in Medical Oncology
	Licensed to practice Medicine in California and Maryland

MAJOR PROFESSIONAL INTERESTS: Relationship between cancer and immunodeficiency states; anti-retroviral chemotherapy

Mr. NATCHER. Thank you, Dr. Broder.

Dr. Broder, sitting to my left is Congressman John Myers, a Member of the full Committee on Appropriations, and one of the best Members that we have on our committee.

He doesn't serve on this subcommittee, but he is very much concerned about this matter, along with all of the other parts of our bill, health and education.

Every year when Carl Pursell and Joe Early and Silvio Conte and the other Members of our subcommittee take this bill to the full committee and to the Floor of the House, our friend, John Myers, always helps us. And I want to say that on the record.

He is one of the best Members that we have in the Congress. He is concerned about it. He sits here with us this morning, and I want you to know, Dr. Broder, who he is.

Dr. BRODER. Sir, I have had the pleasure of meeting him.

PROGRESS AGAINST MORTALITY RATES

Mr. NATCHER. Yes, you re right. And we are glad to have you, John.

Now, Dr. Broder, as you know, Congress has appropriated approximately $18 billion for cancer research since 1971. This is roughly one-fourth of our total investment at the National Institutes of Health.

Doctor, are the American people wrong to have expected more progress than has been made up to this time?

Dr. BRODER. Sir, the American people are quite correct in expecting a high standard of performance from Federal officials. So in that sense, they certainly are correct to have high expectations.

I would argue that there are some areas of significant progress against the death rate for cancer. We have made significant progress for people under age 65, particularly for very common tumors.

For example, in colo-rectal cancer for people under age 65 since 1973, which would be the earliest reference point we would use: there has been a 15 percent reduction in the death rate.

For ovarian cancer there has been a 25 percent reduction. For stomach cancer, the reduction is 25 percent; for bladder cancer there has been a 32 percent reduction in the death rate.

For cancer of the cervix, there has been a 39 percent reduction in the death rate. For cancer of the oral cavity—the mouth—there has been a 20 percent reduction in the death rate. For thyroid cancer, a 26 percent reduction in the death rate.

Those are comparatively common tumors. For Hodgkin's disease, there has been a 52 percent reduction; for testicular cancer—and progress here is extremely important because we can save young men and restore essentially a full, normal life—there has been a 61 percent reduction in the death rate.

So for a number of common tumors under age 65, I believe there is evidence of progress. For people over age 65, I believe nobody can be satisfied with the level of progress, likewise for progress in people who belong to under-served populations, including minorities. For people who are impoverished, I think all of us need to redouble our efforts and do a better job.

Mr. NATCHER. Doctor, can you tell the committee how many Americans are expected to die of cancer this year; and also, if you will, tell us how this number compares to five years ago and to 1973 when the war on cancer began?

Dr. BRODER. Sir, since 1973, there has been a 5.4 percent increase in the death rate for cancer, so the death rate has been going up since 1973, if you look at the total population.

The number of new cases of cancer has gone up 14.6 percent, if you look at the total population. If you are asking how many Americans in 1990 will get cancer, we expect the figure to be 1,000,000; if you are asking how many people have cancer this year, we expect the figure to be a half million.

SURVIVAL RATES

Mr. NATCHER. What has been the overall change in the survival rate for all cancers and all Americans since the year of 1973?

Dr. BRODER. Our best estimate is that in the early 1970s, the chances for a five-year survival, i.e., the relative probability of survival, was approximately 49 percent, taking all cancers.

This has gone up approximately 2 percent in the latest figures, which would be based on five-year survival figures from the early 1980s, a ten-year difference of time. This is the latest set of figures that we have.

YEAR 2000 GOAL

Mr. NATCHER. Five years ago the Cancer Institute announced the goal of 50 percent reduction in cancer mortality by the year 2000.

Dr. Broder, you have been director now for about a year. In your professional judgment, what are the chances of meeting this goal?

Dr. BRODER. I think the jury is still out on this, Mr. Natcher. I think in some areas we are on-track, but I think we do have some problem areas. We can't ignore the problem areas.

The death rate for lung cancer in women, for example, has gone up 100.4 percent since 1973. So in some areas, we clearly have to redouble our effort and re-focus our thinking.

But I would like to stress one point. Some states in the United States for certain common tumors have actually met or exceeded the year 2000 goals.

For example, the State of Utah actually has a lung cancer death rate which is more than 50 percent below the national average, so it has actually achieved the year 2000 goal for this form of cancer.

The states of Wyoming and Utah for cervical cancer have 50 percent or greater reduction in cervical cancer, compared to the national population.

So I believe that these goals are feasible and achievable. They are not pie-in-the-sky types of goals.

I think we should have them, and I will report to the committee at such time as our predictions are that we will or will not make those goals.

I think the jury is still out.

NEW INVESTIGATORS

Mr. NATCHER. How much of your grant funding goes to new investigators, and how much ends up at the same institutions year after year, Dr. Broder?

Dr. BRODER. We have a system called the First Award System, which allows investigators who are coming in to apply for investigator initiated research to compete for a grant for the first time.

By number amounts, approximately 10 percent of the grants in our grants portfolio are committed to this First Award. By dollar amounts, this is closer to approximately 3 percent. This is a very important mechanism, and we hope to give some diversity in our program.

In addition, we give special consideration to individuals who are coming in for a First Award, and where there is any benefit of a doubt that we can give them, we act in their favor.

There is, however, in our grants portfolio, a significant number of grants that go to highly distinguished investigators who successfully compete in the system. Certain institutions have a very high probability of success. However, there is turnover in the system. For example in both 1990 and 1991, over half of the competing grants funded will be awarded as new grants. And so the answer to your question is there is some focusing of grants in certain institutions among certain individuals.

Mr. NATCHER. Dr. Broder, as you and Dr. Raub know, the number of new applications submitted to NIH as a whole has increased dramatically over the last 10 years from about 18,000 to over 20,000.

The number submitted to the Cancer Institute during this period has actually declined from a high of 3157 to about 2900, which is expected in 1991.

How do you explain these numbers, Dr. Broder?

Dr. BRODER. Well, actually, we need to coordinate those figures. Our best estimate is that in the early 1980s, we were at approximately 2900, and we are going up to about 3200 in our latest count.

So we will need to coordinate with the NIH. We think our figures are in line with the other categorical institutes.

Mr. NATCHER. If you will, now, Doctor, insert in the record at this point a table for the period 1971 to 1980 showing the appropriation for the Cancer Institute, the number of cancer deaths, the age adjusted mortality, and the best estimate of the overall survival rate for cancer patients, if you would place that in the record, that will help us, Doctor.

Dr. BRODER. Sir, I would be glad to.

[The information follows:]

CANCER STATISTICS FOR THE PERIOD 1971-1990

There is a long-term history of cancer mortality increasing in the United States. Cancer mortality has been increasing at least since 1950 and even since 1971 there is still an increasing trend; the cancer mortality rate in 1990 is estimated to be eight percent higher than the rate in 1971. Since the size of the U.S. population has increased and there are an increasing number of older Americans, this eight percent change in the mortality rate translates to a 50 percent increase in the numbers of cancer deaths between 1971 and 1990. Because of the inherent lag in obtaining mortality data, 1987 is the most recent year for which complete figures are available. Our receipt of relative survival figures is also delayed because of the need to follow patients for a given number of years following their initial diagnosis, and the necessity of linking these figures with mortality records.

YEAR	APPROPRIATION	NUMBER OF CANCER DEATHS[2]	AGE-ADJUSTED RATE (1970 STD)[2]	RELATIVE SURVIVAL[1]	
				2-YEAR	5-YEAR
1971	230,383,000	335,968	161.89		
1972	378,794,000	345,961	163.41		
1973	492,205,000	349,563	162.01	56.6	46.0
1974	551,191,500	358,925	163.10	59.0	48.4
1975	691,666,000	364,095	162.24	59.5	49.1
1976	761,727,000	375,658	164.50	59.8	49.5
1977	815,000,000	384,872	165.11	60.1	49.4
1978	872,388,000	395,099	166.08	60.2	49.4
1979	937,129,000	403,356	166.08	60.1	49.2
1980	1,000,000,000	416,481	168.13	60.6	49.4
1981	989,355,000	422,042	167.27	61.3	50.4
1982	986,617,000	433,731	169.13	61.2	50.1
1983	937,618,000	442,923	169.68	61.9	-
1984	1,081,581,000	453,450	171.07	62.0	-
1985	1,183,806,000	461,520	171.25	62.9	-
1986	1,258,159,000	469,330	171.33	-	-
1987	1,402,837,000	476,894	171.49	-	-
1988	1,469,327,000	487,359*	172.82	-	-
1989	1,593,536,000	496,478*	173.50*	-	-
1990	1,664,000,000	505,597*	174.18*	-	-

[1] Source:NCI SEER Program (1973-1987)
(Followup data available for years 1973-1986)

[2] Source: National Center for Health Statistics

* Estimate based upon actual values from years 1971-1987
(Linear regression using principle of least squares)

NOTE: Appropriation amounts have not been adjusted for enacted rescissions, administrative reductions, and supplementals.

NEW EMPHASES

Mr. NATCHER. What changes have you made as director in the overall approach of the Institute to its mission, Doctor?

Dr. BRODER. Sir, I believe that we need to give a greater emphasis on prevention, control, community service, outreach and knowledge dissemination.

I believe that in the coming decade, we must give a greater emphasis to these areas. We need to do a more effective job of transferring the knowledge that we have, to ensure that it diffuses to all Americans so that they can take advantage of all of the new information we have on prevention, early diagnosis and treatment.

And so those would be a new emphasis, particularly to information services which I think are key to the success of our mission.

Mr. NATCHER. Dr. Broder, as you know, this is the first budget request which has been prepared entirely under your direction.

Are there any significant changes which you are recommending to the budget, either different program emphasis, or a switch in the allocation of funds among the various mechanisms?

Any changes, Doctor, that you would want to talk to us about that are not set forth in your justifications and in your budget request?

Dr. BRODER. Sir, are you asking my professional needs?

Mr. NATCHER. No, as far as the 1991 budget request is concerned, you don't show any significant changes in your budget material. Are there any that you would like to talk to us about, Doctor?

Dr. BRODER. Well, internally, yes. For example, we have made changes in our cancer information service program, which I think is extremely important and handles about 500,000 calls. We have about 30 states covered in providing direct community access to the population and answering questions relating to cancer or giving specific advice to patients and their families.

That program went from $4.8 million to approximately $8 million. We have gone from covering about 150,000,000 to about 164,000,000 Americans, using community-based support systems.

We think that this is an exceedingly important activity and is emblematic of the kinds of commitments we want to make.

I would also like to say that we made an important change which is not directly reflected in the budget, but which will be reflected in the kinds of operational activities we do. We added an important new criterion onto our comprehensive cancer centers: community service and outreach activities. And this is a formal criterion now.

The Congress has, in language over the years, asked for this to be done, and during the last year we have embodied this in our definition of comprehensive cancer centers; and therefore, we will expect to see that the cancer centers' program will be having more community service, more outreach and more of a specific effect in the communities that they serve, as well as the Nation as a whole.

CANCER CENTERS

Mr. NATCHER. Doctor, as you know, your budget includes $103,000,000 for centers, which is essentially the same as last year.

Are you satisfied that within the total being requested that this is the appropriate allocation to centers?

Dr. **Broder**. The centers are an important foundation stone. With that particular budget, we will face the following choice: We will face the choice of downward negotiating centers or phasing out certain grants.

I would hope that we can achieve some measure of flexibility so that within that budget we would be given as many options as possible to maintain excellence in the grants portfolio. This will require the appropriate balance between downward negotiation and actual, regrettable but necessary, phase out of cancer centers so that the excellence of the total portfolio can be maintained.

We are concerned about excessive reductions in order to maintain a specific arbitrary number. And within available funds, it might be better under some circumstances to actually phase out certain centers rather than downward negotiate, impinging on the excellence of all centers.

INTERNATIONAL ACTIVITIES

Mr. **Natcher**. Doctor, sometimes we receive letters from people around this country and sometimes from abroad that maybe we are not working together in this country and around the world to get the information that we have out to practicing physicians.

How do you feel about it, Doctor? You know what I am talking about?

Dr. **Broder**. Is the question, are we getting adequate information disseminated?

Mr. **Natcher**. Well, yes, and are we finding out what other people are doing, not only in this country, but abroad?

Dr. **Broder**. I think we consider our international activities very important. We have several bilateral agreements with a number of countries. We have science exchanges. In addition, there have been a series of unforeseen events in Eastern Europe which could not have been put in anybody's planning schedules and therefore would not necessarily appear in any budget document. These events provide unprecedented opportunities for information exchanges in both directions involving some countries in Eastern Europe and also the Soviet Union.

I have met personally with Ambassador Yuri Dubinin of the Soviet Union, and we have achieved at least a preliminary understanding of new information exchanges that will occur.

So the answer to your question is, I think, it's an important topic. I think we also need to refine and do better, but I think we are on the right track.

Mr. **Natcher**. Thank you, Doctor.

Mr. Pursell, I yield to you.

RISING INCIDENCE RATES

Mr. **Pursell**. Mr. Chairman, I am in a predicament here. I am one of the junior Members, but ranking on the Republican side today, but I serve on another subcommittee named Energy and Water. And it happens to be my chairman is sitting to the left, Mr. Myers, so I would be very happy to yield to you, John, if you have some questions you would like to ask or comment before I ask any questions.

Mr. **Myers**. Well, thank you, Carl.

From personal experience, I do have knowledge of Dr. Broder and his staff. My wife was diagnosed in early January as having cancer, and we did go out to NCI, and the staff was extremely cooperative.

I do thank the staff, all of you, for the efforts, the consultation you gave. She elected to go elsewhere to have her treatment, but we do appreciate your help very much.

Dr. **Broder**. Sir, in effect she didn't elect to go elsewhere. We had a program amputation that moved NCI staff en mass to the Lombardi Cancer Center at Georgetown University.

Mr. **Myers**. Well, she is at the Cancer Research at the Vince Lombardi Center which she had read about, but I do appreciate your help very much, and now I have some personal information.

You know, cancer is something that happens to someone else. That has been my experience, anyway. Friends have had cancer, but it never struck in my house. Well, it's come to our home now, so I have a new interest in it. I do appreciate the invitation that this subcommittee gave to let me sit in and hear you—I do have one question I may ask.

The incidence of cancer, as you reflected here, is going up in the population. Is that because we have better diagnosis today, or is the frequency of cancer in our population really increasing?

Dr. **Broder**. It's probably both. There are times when a new technology becomes available. For example, new ultrasound or magnetic resonance imaging techniques or some new surgical test or some way of identifying people who are at an earlier stage of cancer development might come into play.

If mammography comes into a community that never used mammography, you may have an artificial increase in the apparent number of cancer cases, i.e. temporarily, a blip in the cancer curves would take place. But that would eventually come back down to base line.

I think that is in part an explanation for the apparent rise in incidence in this country, that is, we are doing earlier diagnosis and more diagnosis. But I do not believe that is the total explanation.

I believe that the bottom line is that the incidence of cancer is going up in real terms.

MAMMOGRAPHY TRAINING

Mr. **Myers**. You mention mammography, and certainly I support it. However, it's not one hundred percent accurate.

Is there any evidence or anything being done to train the readers of x-rays around the country to more properly read mammograms?

From personal experience, I know a mammogram is frequently taken, but the result is no better than the person reading it.

Is there any evidence that mammograms are being misread around the country?

Dr. **Broder**. Sir, no technology is better than the people who read it, and we believe that people are also the most important resource.

I feel that in mammography, the NCI has a strong interest in both the quality of care and the proper implementation, so there are a number of issues relating to standards of care and standards of training that we become intimately involved in.

We have invited representatives of the electronics industry to meet with us. They have met with our division of cancer biology diagnosis and centers, which is run by Dr. Alan Rabson. We have involved representatives of the entire electronics industry and asked them to help us. We put to them the challenge of coming up with better, more effective mammography equipment that could be more portable and more user friendly to help address some of the issues that you are concerned about, such as minimizing the chance for error.

And we feel that American engineering, in cooperation with the Cancer Institute, might be able to have a positive effect here. And we are trying to stimulate research and if appropriate, do cooperative research and development agreements in this important area.

Mr. **Myers**. I appreciate your taking the time, Joe, and the committee Members who sit here every day. I just came in here as a camp follower.

But what concerns me is the fact that women all over the country are spending their money and depending upon the results from a mammogram. Yet if the person reading those mammograms is not properly trained or doesn't know how to read them, how do we better train them? How do we get it across that these people have to do a good job?

Dr. **Broder**. That is why we have made a strong emphasis on information services, which broadly defines and encompasses some of the issues that you are talking about.

We want to make sure that we are getting appropriate information about standards of care and standards of excellence.

The points you are bringing up for breast cancer are extremely important and quite valid, but they do not end there.

For example, Pap testing. Most women who die of cervical cancer are dying of a completely preventable disease. We have recently spent an enormous amount of time and attention and resources to help standardize cervical screening.

We have come up with the Bethesda system—I wanted to call it the Broder system, but the Executive Committee knocked it down—for developing standards for appropriately reviewing Pap smears so that they could be read in a standardized way.

So the point you are raising is extremely valid, extremely—none of the technology of the Cancer Institute is of any use if people don't have the know-how to apply it. This is an extremely important area and one reason among many why we are stressing information services, broadly defined.

Mr. **Myers**. Thank you.

Mr. **Natcher**. Mr. Pursell.

Mr. **Pursell**. Mr. Myers, I sort of sense you would like to be on this committee, right, John?

This is a great committee.

Mr. **Myers**. I might add, I served with your chairman many years ago on another subcommittee. We have been friends for a good many years, more years than he would like to admit.

CANCER EDUCATION

Mr. **Pursell**. Gathering from your remark reading your public statement and looking at the budget, I have a feeling that there is something out of balance in terms of good research, intramural, extramural, 18 billion has been spent on research in cancer over the last few years, as the chairman outlined, but I alluded, Dr. Broder, that the public education sector is way behind in terms of people taking advantage, both men and women, in the area of prevention.

And when you look at your budget, in my budget book on Page 41, cancer prevention and control, you have got 138 people, you are adding 17, this is from 1989, last year I think you had 148.

So you are getting seven additional people in that category, and then on an earlier page, on Page 40, in cancer education, we are talking about, I got a figure here of $2.9 million; is that correct?

Dr. **Broder**. That is correct. $2.9 million was budgeted for the cancer education program for 1989, sir.

Mr. **Pursell**. Why is that so low? I mean, if we have got the research on the record, and we know the facts, why can't we get the rates down in areas where we have been successful in getting these breakthroughs and yet the public is not aware? There is a major gap there, as I feel, between the results that are truly tested, distributed, but we are not getting them out to the public, both men and women alike.

What is the problem here?

Dr. **Broder**. I agree with your point, and that is one of the reasons why we are stressing certain information services, e.g. cancer information services involving our electronic data bases that allow physicians to interact with us and get the latest information.

But there are several types of activities that are not technically encompassed entirely within the budgets that you have seen.

For example, an enormous amount of prevention, early diagnosis and as I mentioned, community service and outreach, would be subsumed within our cancer centers budget, which is approximately $103 million.

CANCER CENTERS

Mr. **Pursell**. How much in the cancer centers?

Dr. **Broder**. Approximately $103,000,000.

Mr. **Pursell**. For education?

Dr. **Broder**. Well, the grand total is about $103,000,000.

Most cancer centers would be expected to have those activities, especially the ones that are designated as comprehensive and clinical. Eighty percent of our cancer centers fall into these categories and would be expected to have significant activities in education, training, and outreach activities.

Mr. **Pursell**. Doctor, I will tell you in my congressional district there are 20 people that could tell me where the cancer centers are. Does that surprise you?

Dr. **Broder**. It doesn't surprise me.

Mr. **Pursell**. Except the professionals who are at the University of Michigan.

Dr. **Broder**. That is my alma mater; and therefore, I can say it's a good place. I don't know what Washtenaw county is like now. But it would seem to me that I would find it very sad indeed if people in the surrounding areas didn't know about their cancer center.

INFORMATION SERVICES

Mr. **Pursell**. Well, I use the number 20, but I am trying to make a point here that our education component is so low here in the budget of $2.9 million compared to where we are, where the information that is readily available to the general population, there is a big gap here between the centers and NIH and the general public.

And somehow we have got to find a way to bridge that gap. And I am not sure electronic and computerization and all of that is going to do it.

There is something fundamentally——

Dr. **Broder**. I agree with you.

We are putting approximately $92,000,000 total in the information services within the Institute, but I take your point that we need to be more effective in cancer information services across the board. And that is why I listed it as one of the areas where we will give greater emphasis.

Mr. **Pursell**. It's not reflected in the budget; that's the point I was trying to make here, at least it doesn't show in the numbers I see here.

Dr. **Broder**. Cancer information dissemination is contained in many of the mechanisms, so——

Mr. **Pursell**. You don't add one dollar to last year's budget on cancer education. Last year was 2.9, and this year it's 2.9, same number.

Dr. **Broder**. For example, not necessarily reflected in that budget line, but in fiscal year 1989, we put in $4.7 million as a funding level for our cancer information services. The CIS program is one way that people can call our 1-800-4-CANCER number to get a lot of information. That covered 141,000,000 people.

The funding level for fiscal year 1990, as a result of reprogramming, was $8 million, and we could then potentially reach 164,000,000 people using community-based support programs.

We have been able to provide cancer information services to Kentucky, Louisiana, Mexico, North Carolina, Puerto Rico, Ohio, Oregon, Rhode Island, South Carolina, Utah, Virginia, Wyoming; some of these areas are specifically targeted for rural population where we think there is an especially high need.

In the State of Virginia, we are experimenting with a cancer information service which is targeted to people who have comparatively impoverished educational skills; getting information services to people who may not have the most comprehensive reading skills is not an easy task.

And we are trying to learn how to do that, and as we learn how to do that from appropriate pilot projects, we will expand those activities.

But I do take your point. We do need to do a better job on this area.

COMMUNITY CLINICAL ONCOLOGY PROGRAM

Mr. **Pursell**. Maybe we need some really brainstorming, creative thinking, because there are no institutions in a given community that can put out that kind of information, except at the state level or maybe sophisticated county where you have a public health center and then they put out information on hundreds of diseases and problems in the area of cancer, which is an extremely successful breakthrough over the last few years.

And I agree with those statistics, our general public is not picking up on the opportunities in the area of prevention.

So the educational component here budget wise, if you were to add dollars there, or double that program, where could we take the money from?

I know you don't have any discretionary funding, but maybe you should have. I think some of the directors ought to have a little discretionary funding, or at least NIH director, whoever that shall be some day.

Dr. **Broder**. Sir, I promise you that within available funds, we will make information services an important priority. There are several kinds of activities that are not covered in any one mechanism.

We have a community clinical oncology program. We also have certain outreach activities, including for example, some of our satellite programs for accruing patients to clinical trials, and a new minority accrual initiative in our cancer therapy evaluation program, which is specifically targeted to under-served populations with high cancer risks. These do not necessarily appear in those numbers.

They might be subsumed within the larger budget of cancer treatment, but they involve specifically targeting and represent a kind of outreach, and in the broadest sense of the term involve information capacity, but I do take your point.

CANCER EDUCATION AND TRAINING

Mr. **Pursell**. Well, I haven't got a good answer yet. Is cancer education the same as last year?

Dr. **Broder**. Yes, sir. Cancer education involves the R-25 mechanism, which is basically a kind of training grant for health care providers, so that they will become interested in cancer or expand their skills—we have a strong emphasis on prevention.

INFORMATION DISSEMINATION

Mr. **Pursell**. Where's your big budget dollars and personnel in terms of getting that dissemination out to people, both in rural and urban areas?

Dr. **Broder**. That is within the $92 million figure. I will be happy to submit for you for the record new major activities supporting fiscal year 1990 that have to do with information services. Some of these things have been as a result of internal reprogramming from the discretion that we have.

We cannot reprogram for areas that are programs, projects or activities—PPA—but there is some leeway for reprogramming activity. In our fiscal year 1990 estimate we are spending about $92.4 million in the total context of information dissemination.

I promise you that it's not solely on computers and things like that.

Mr. PURSELL. Give me the big figures out of the 92,000,000; where are the big pieces going?

Dr. BRODER. Okay. Approximately $8,000,000 is going to our cancer information service, which is a significant increase over the 4.7 million that had been in the previous fiscal year.

We have approximately $32 million in targeted behavior modification protocols to help people develop better types of lifestyle and prevention strategies for their own lives. This would include smoking cessation efforts, on which approximately $17.4 million is being spent

Mr. PURSELL. Who is putting that information out and in what form?

Dr. BRODER. The Division of Cancer Prevention and Control is principally responsible for that. It has several programs, one called a COMMIT Program and one called the ASSIST Program.

Mr. PURSELL. At one center?

Dr. BRODER. No, sir. That is throughout the country

Our Assist Program will eventually be targeted, will try to reach 50,000,000 Americans and will have intensive education, in cooperation with state and local health agencies. We will have a cooperative agreement arrangement.

And in addition, we will also be working with the American Cancer Society to make sure that we are coordinating our efforts.

Mr. PURSELL. The Public Health Department and the states and the counties have virtually little impact on the communities. We don't really have a marketable vehicle there at the local level.

We do have it at the state, as I mentioned earlier, some county levels. But there is a major gap there of, you know, the schools, the parent teachers associations, or community based service programs, to get that information out where it should be targeted.

I don't know. Well, break that out for me; would you do that, the 92,000,000, how it's used and where it's used and personnel involved, let's take last year and this year.

I would like to look at that—since you have been there a year, you said you have made some changes legitimately.

Dr. BRODER. We will highlight the areas that we do.

[The information follows:]

INFORMATION DISSEMINATION

The following represents NCI's $92 million portfolio of information dissemination activities for the FY 1990 estimate. Activities supported in FY 1990 are increased nearly $4 million over FY 1989.

Dollars in millions:

	1989 Actual	1990 Estimate
Behavior modification studies in smoking, breast and cervical screening, special minority-focused activities, worksite and physician intervention trials, diet, and avoidable mortality studies	$32.3	$32.4
Cancer Information Service (CIS)	4.7	8.0
Public health department initiatives	3.4	3.7
Published manuscripts under research project grants	7.2	7.8
Information and statistical support for clinical cooperative groups	4.6	4.6
Clinical Cooperative Group Outreach (CGOP)	3.3	3.3
Drug development support including information systems supporting drug screens for both cancer and AIDS	4.1	4.1
Outreach activities under cancer center grants	1.8	2.0
International activities, including scientist exchange	0.6	0.8
Conference support	0.3	0.3
Computer, library and clearinghouse services for Physicians Data Query (PDQ), CLINPROT (a database listing describing over 7,400 clinical trials conducted throughout the world), and the Cancer Prevention and Control program	12.1	12.2
Personnel, management and support costs, including those of the Office of Cancer Communications	14.1	13.1
Total, NCI	88.5	92.3

NCI is very committed to the dissemination of information to both the lay and professional communities and will continue to hold the support of information dissemination activities a high priority within the Institute.

Dr. BRODER. I would like to say that your comments are well taken and have been acted on. For example, we have six regional coordinating centers now as part of the Black Leadership Initiative which is specifically targeted to galvanizing community resources to help the problems of certain minorities and under-served populations.

This has been effective in some areas in mobilizing the community, for example, the City of Philadelphia, thereby increasing awareness and sensitivity to a number of preventive and health care issues.

And that model of involving community and community leaders is also something appropriate that we may wish to expand. And in the technical sense, the Black Leadership Initiative might not be considered as an information service but in the sense that you are using that term, it is, and that is a new initiative within the Cancer Institute.

Mr. PURSELL. My last quick question, do you think your recommendations next year will be more advanced in this particular area in terms of priority?

You cannot do a lot the first year.

Dr. BRODER. Sir, I can promise you that the professional judgment budget which I submit will certainly reflect that.

Mr. NATCHER. Mr. Early, I yield to you.

GRANT PAYLINES

Mr. EARLY. Thank you, Mr. Chairman.

Dr. Broder, it's good to see you back.

Your pay line in 1980 was, I understand, 218; is that right?

Dr. BRODER. In 1980?

Mr. EARLY. Yes.

Dr. BRODER. We were funding approximately 38 percent of grants.

Mr. EARLY. The pay line was 218?

Dr. BRODER. That is correct.

Mr. EARLY. So your pay line has gone from 219 to 197 to 193 to 181; in 1988 it was 158. What is your pay line for 1990, Doctor?

Dr. BRODER. Sir, not to introduce a complexity, but we are not using the old pay line system, but broadly speaking in answering your question, the pay line would actually be more severe than what you have just described.

We now use percentiles.

Mr. EARLY. All right.

Could you estimate what that percentile would be in terms of a pay line?

You can provide those figures for 1990 and 1989, for the record please.

Dr. BRODER. Certainly.

Mr. EARLY. I think I know why you changed it, but I really don't like to——

[The information follows:]

PAYLINES FOR RESEARCH PROJECT GRANTS

NIH currently reports grant funding rates using percentiles which indicate the scientific merit of an application relative to all other applications reviewed by the current plus two prior meetings of a study section. The percentile then becomes the score through which applications are to be funded. Percentiles apply to a portion of research project grants: the traditional RO1, MERIT and FIRST awards. The remainder of the research project grants: Program Projects, Outstanding Investigator Awards, Small Business Innovative Research Awards, Cooperative Agreements and Requests for Applications are funded using priority scores as the payline determinant. Based on this, NCI would have to estimate its payline for FY 1989 and FY 1990 as 166 and 160 respectively. These are significantly more austere than in the late seventies or early eighties.

Dr. BRODER. That was an NIH policy, sir.

DOWNWARD NEGOTIATIONS

Mr. EARLY. I know it was.

What will the downward negotiation for the non-competing grants be for your institute?

Dr. BRODER. In fiscal year 1991, we expect for competing grants 20 percent downward negotiation; and for non-competing grants, approximately a 4 percent downward negotiation.

Mr. EARLY. Doctor, for competing grants, in 1988, there was an 11.7 percent downward negotiation; in 1989, 13.5 percent; for 1990, 10.2 percent.

Now you are talking about 20 percent. Now, this committee has listened to professionals such as yourself tell us that 10 percent downward negotiation would be the critical point. What has happened?

I've heard this for the last three years. Now you are suggesting 20 percent. Do you think 20 percent is dangerous?

Dr. BRODER. I think 20 percent downward negotiation significantly depreciates the value of peer review.

Mr. EARLY. There is no good scientific reason for such a large reduction; is there, Doctor?

Dr. BRODER. This downward negotiation is not predicated on a scientific reason.

Mr. EARLY. That is my question. So the answer is no; right, Doctor?

Dr. BRODER. The answer is there is no scientific reason that is involved in this.

Mr. EARLY. Fine.

For the record, tell me how the amount was arrived at and, what kind of effect these reductions are having on research project grants.

[The information follows:]

DERIVATION OF NEGOTIATIONS TO RESEARCH PROJECT GRANTS

The overall policy guidance for the FY 1991 President's Budget was to maintain the same total number of research project grants that were funded in 1990. In order to accomplish this, and to provide some program balance to other NCI mechanisms, a decision was made to support research project grants below the peer reviewed amount.

The mix of negotiations between noncompeting and competing grants was an NCI determination. The decision to reduce noncompeting grants by four percent addressed the issue that these grants were previously cut in their competing year, with a comparable reduction to the outyear amounts. Any further reductions to them in their noncompeting year compounded their reduction to the point where more cuts were thought to be severely deleterious to the success of the project. In addition, noncompeting grants are generally provided an inflationary increase of approximately four percent when they reach their noncompeting status, so the reduction of four percent, on the average, would fund these grants at the current level of support.

On the other hand, competing renewal grants oftentimes receive recommended levels increasing these grants greater than 20 percent when they recompete. It was felt that the reduction of 20 percent would keep these grants, on the average, at their current level of support. For new grants, as those grants are just getting off the ground, the 20 percent reduction could have an extremely high negative impact. The Institute will be trying to handle these awards on a case-by-case basis to assure that the new investigator, whose grant is generally smaller, can be funded at a sufficient level to undertake their research effort.

The issue of negotiations to grant-supported programs is one of continuing concern within the National Cancer Institute, which believes that some balance needs to be made whereby the best science is supported within the Institute's total availability, irrespective of numbers of projects supported. Downward negotiations depreciate the value of peer review.

INSTITUTE OF MEDICINE REPORT

Mr. Early. Now, I want to pursue what the chairman had talked about, the centers. The Institute of Medicine has completed an analysis of the cancer centers program. Will you briefly summarize the IOM's findings and the recommendations, particularly with regards to resources?

Dr. Broder. Sir, in brief, they made several recommendations. Among them was that the centers program should receive a higher visibility, that the centers program be moved administratively from the Division of Cancer Prevention and Control to another operational unit of the NCI, that approximately $6,000,000 be found immediately to be put into the centers program, that a five-year plan for centers be established, and that appropriate levels of dialogue and interaction with the center's community, with the principal investigators and other members of the centers and NCI staff be undertaken.

Mr. Early. Would you agree with every one of those recommendations, Doctor?

Would you agree, but in different degrees perhaps with all the recommendations?

Dr. Broder. Within available funds we have attempted to implement all of the recommendations.

CANCER CENTERS

Mr. Early. I am not talking about within available funds. I am talking about the funds you don't have, Doctor.

Doctor, in 1988, NCI was supporting 60 centers; correct?

Dr. Broder. That is correct.

Mr. Early. In 1990, centers will be phased out; is that correct?

Dr. Broder. Last year we terminated four core programs.

Mr. Early. So in 1989 and 1990 an estimated 10 centers will be phased out?

Dr. Broder. We received language in the last appropriations bill which strongly gave us an advisory that we should keep the numbers of centers constant.

Mr. Early. I have a tremendous problem with that, just the way you responded to the Chairman's question.

The justification indicated that NCI will support 56 centers in 1990 and 1991 at a proposed funding of $103,000,000; is that correct, Dr. Broder?

Dr. **Broder**. Yes, sir.

DOWNWARD NEGOTIATIONS FOR CENTERS

Mr. **Early**. That is less than a one-half of 1 percent increase. Will this permit the level funding necessary to ensure the critical role of cancer centers?

Doctor, in your summary to the chairman, you said the downward negotiation is getting threatening. It's going to mean phasing out of specific services, and you asked for autonomy, which I think you should have.

I think you were being honest. Don't we have to make a decision and say that we cannot keep downward negotiationing at this rate?

Dr. **Broder**. I agree with you, and many of our advisors agree with you, that downward negotiations beyond a certain point will nullify the peer review process and threaten the excellence of the entire portfolio.

Within available funds, I believe we should have the discretion to make the best accommodation possible, and downward negotiation may not be the best solution.

Mr. **Early**. I think you and the other directors qualify your comments too much, as far as within available funds. That is the committee's jurisdiction, and the Administration's.

You said to the Chairman that the excellence of the centers would be maintained. You cannot, Doctor, if you keep going with this type of downward negotiation, can you?

Dr. **Broder**. There is no question that downward negotiations or limitations on resources do have an effect on our cancer centers program.

The cancer centers program is among the most important, crucial foundation stones of the National Cancer Program.

Mr. **Early**. Don't you think they could be a lot better, too, Doctor, with the adequate resources?

Dr. **Broder**. There are many opportunities that we could pursue in our cancer centers program.

Mr. **Early**. What was your original request to the Department for Cancer Center Core grants?

Dr. **Broder**. Sir, the original request was about $41,000,000 above what is shown in the budget that I am defending today.

PROFESSIONAL JUDGMENT

Mr. **Early**. In your professional judgment, how much is necessary to retain the centers program at an appropriate level of funding and stability?

Dr. **Broder**. Approximately $144,000,000.

Mr. **Early**. Do the centers with approved priority funding have adequate support available for the core centers?

Dr. **Broder**. Yes, sir.

Mr. **Early**. Would additional funding for cancer center core grants be a funding priority in your professional opinion?

Dr. **Broder**. Yes, sir.

PROTON BEAM RESEARCH

Mr. **Early**. I appreciate your answering the questions, Doctor.

Chairman Natcher said he has here his good friend, Mr. Myers, who is everyone's good friend. John Myers isn't a typical guy that throws money at every program. He is very conservative, and he doesn't say it's important to me, too often. He's the Ranking Member on the Energy-Water Subcommittee.

I read an article in this morning's paper about the supercollider. We talk about all the money Defense gets and now the Energy Department. DOE is projecting a $2,000,000,000 overrun, a $2,000,000,000 overrun on this project, and the Administration is behind it.

The article says that it was estimated that D.O.E. would spend $6,000,000,000, but now it is going to spend a lot more than that.

Doctor, last year, $500,000 was included for proton beam centers; NCI was to conduct a review and solicit applications.

Now, is that on course?

Dr. **Broder**. Yes, sir. We have a request for applications out. We would expect that we will be able to process them, and we would expect that before the end of the fiscal year we will have the applications reviewed.

And we would expect that one or more grants would be funded.

PHOTODYNAMIC THERAPY

Mr. **Early**. Every one on this committee knows how difficult that is, Dr. Broder, because the budget doesn't have enough money for other things

I also don't think you do nearly enough research with regard to lasers; and again, it's a shortage of money.

However, the article in the *Post* said, "The changes in the supercollider include a one-mile expansion of the circular tunnel in which beams of protons will be steered into head-on collisions yielding dense concentrations of energy. It will now be 54 miles. The magnets needed to steer the beams also will be modified, and the energy of the proton beams will be increased to make sure that adequate collisions occur."

I see potential in that type of research, not physics or energy, but medical research using energy, and you don't seem to have any funding for that.

Mr. Natcher, last year, we made one of our breakthroughs for the mentally retarded with money that was in SDI. How can Defense, and now Energy, get money for this type of expansion, while you have a budget where when asked is that enough, you say, well, instead of just saying no, it's not enough. It's tough, Doctor, it's tough.

I spent a lot of time visiting at the Wellman Institute. Do you have an opinion about the potential of lasers with regards to cancer, Dr. Broder?

Dr. **Broder**. I think it's a highly interesting and innovative approach. We are, in fact, pursuing it. We are combining laser therapy by also giving porphyrins, which are substances that can get into tumor cells. And once they are in there, they will actually absorb a path of light which a laser can deliver and in effect destroy a cancer cell.

Also we are able to use luciferin, which is a chemo-luminescence substance actually similar to the protein which permits fireflies to give off light. We will be able to adapt that technology to kill tumors using light, packages of light from lasers and other sources to kill certain cancer cells.

We use it, for example, to open airways that have been closed off in certain forms of lung cancer. There are other related technologies for treating ovarian cancers where one can shine a beam of light and can deliver it to hidden cancer cells.

So that is a high priority area, and I agree with your assessment.

Mr. **Early**. There is not a lot of money for it. This business is money.

Dr. Raub testified the other day about tracing genes and gene signaling and crystallizing, and I am all for that as a layman, it sounds good. That is what you are supposed to do.

But I think that the real advances in cancer treatment are going to come with proton beams and lasers, and in my opinion there is just not enough of effort here, Dr. Broder.

Would you agree or disagree with that?

Dr. **Broder**. Sir, there are many opportunities which exist and which we would like to pursue.

Mr. **Early**. I used my 10 minutes, but I would like to come back for additional questions.

Mr. **Natcher**. Mr. Porter, I yield to you.

BY-PASS BUDGET

Mr. **Porter**. Dr. Broder, this is kind of a strange procedure; isn't it? You submit your thoughts as to what you really would like to have in your bypass budget, and then NIH submits a much scaled-down budget, and then OMB scales it down further.

And then you come back here and have to defend something far less than you really want to have—and have to be beat up by us for having defended less than you really want. It's very strange.

Dr. **Broder**. Our salaries are compensation for that.

Mr. **Porter**. And not nearly enough; right?

Mr. **Myers**. Don't put that in the record.

Mr. **Hoyer**. He just meant it was sufficient for that, not for any of the rest of the work he does.

Mr. **Porter**. Dr. Broder, you prepared a bypass budget that is, if my memory serves me right, something like 2.2 or 2.3 billion.

Dr. **Broder**. Sir, it's $2.4 billion.

Mr. **Porter**. Which is really what you would really like to have in your heart of hearts.

Can you tell us how many more research grants a budget like that would fund? How does that compare with the budget you are going to have to work under?

Dr. **Broder**. Sir, we are required by statute to prepare a bypass budget which is submitted to the President. Under that bypass budget, we would fund over 1500 new and competing grants, which is approximately, roughly speaking, a doubling of the number of grants that are in our system now.

Mr. **Porter**. So for $750,000,000, we would be able to double our research grants.

Dr. **Broder**. That is one of the things which is inherent in that budget, but there are other things as well.

Mr. **Porter**. What else?

Dr. **Broder**. We would be able to have a significant expansion of our cancer centers program; we would be able to encourage them to pursue and in fact allocate more resources for community service and outreach activities within the centers program as I have suggested.

We would have an additional $35,000,000 for our cooperative group program. This is a critically important clinical trails network which is the basis upon which we generate new knowledge for new drugs.

For example, the levamisole, 5-flourouracil combination is adjuvant therapy to help reduce the death rate from certain forms of colon cancers. This was singularly an achievement of that program, and there are many others.

We would have approximately an additional $55,000,000 in our intramural program and an additional $81,000,000 for cancer prevention and control to get into some of the issues that we have heard expressed today which would allow us to have more community-based, action-oriented programs.

We have some models already. We have recently funded a grant in Hawaii in the Waini Coast community cancer center to address the needs of native Hawaiians who have an astonishing high death rate from cancer. We are using a concept of Kokua which is a concept of local social support and interaction. We use that cultural concept to help develop women's awareness for breast cancer and cervical cancer.

We are using the social fabric that exists in a given community, and we hope that that will be a model for how we can interact using the community itself to address its own problems.

In addition, there would be approximately $60,000,000 in construction to help rebuild and refurbish the infrastructure of science in this country.

Mr. **Porter**. We can do all of this if we would just forego one B-2 bomber; perhaps.

Dr. **Broder**. Sir, I don't know what a B-2 bomber costs.

Mr. **Porter**. They estimate that about $500,000,000, but you and I know that they come in at $750,000,000.

Well, I hope—I think I am agreeing with the gentleman from Massachusetts that we really need to rethink our priorities sometime soon and determine if we can't move some funds where they would really allow us to address our biomedical research needs in a much stronger way than we have been able to do in the recent past.

And I hope that we can get to your bypass budget some time soon and pass it and have you get that kind of support that you really need to expand the research activities.

TROPICAL PLANTS FOR DRUG DEVELOPMENT

Let me ask you if you would talk for a minute about the program that you have on investigating tropical forest plants as a source of potential cancer and AIDS drugs? What are you doing there? Is it showing any promise? How are you going about it?

Dr. BRODER. This is a very exciting area. It's the tradition of the Division of Cancer Treatment to pursue activities regarding natural products and biological agents.

It turns out that natural products derived from terrestrial plants, marine plants and certain marine organisms, may have very powerful biological effects and introduce unexpected activity against certain types of cancers, and in some cases the AIDS virus. These natural products in some cases can have activities that we could not have deduced from first principles or in some cases have chemical structures that are quite novel and astonishing to chemists and would not have been things they would have thought of synthesizing.

So the National Cancer Institute is making it a very high priority to make sure that we have a library of appropriate biologic and natural products, and that they are appropriately stored and cataloged.

In some cases, we are working out appropriate arrangements to reach areas of endangered tropical forests and to ensure that we have at least representative access to certain materials. We feel that there is already a great deal of promise in this area.

Many of the drugs and materials that have come out of this program, at least on a preliminary basis, are showing some interesting effects. And this, in my opinion, will be a significant aspect of future research.

A high percentage of the new treatment ideas we bring into what is called investigation of new drug applications are no longer synthetic drugs, but rather they are biologic or natural products or at least things that derive an intellectual linkage from that natural products program.

Mr. PORTER. I understand that you have got the Missouri Botanical Board and New York Botanical Garden and University of Illinois in Chicago all working on this.

Dr. BRODER. We have arrangements with several groups.

INTERNATIONAL ACTIVITIES

Mr. PORTER. And what countries are they working in?

Dr. BRODER. Well, staff and appropriate collaborators and individuals who cooperate with us are focusing on many parts of the world. Important work is being done in Brazil and in the Red Sea.

We have sent NCI investigators to Australia and to certain areas of the South Pacific. We have focused on certain areas of South America, certain of the tropical forests in South America and in regions within Brazil and Panama, for example. So I think that there is a widespread effort to develop this approach.

We are not necessarily prejudging and focusing on only one geographical area.

Mr. PORTER. You have identified this as a very important potential source of anti-cancer and anti-AIDS drugs. What do people in your part of the scientific community do to weigh in on the issue of tropical destruction? Obviously as the tropical forest is destroyed, the chance of recovering these kinds of drugs diminishes; and tropical forests are being destroyed at a fairly rapid rate.

Dr. BRODER. Every scientist who I know and respect is profoundly disturbed by this trend, to the destruction and deforestation of important, irreplaceable, precious areas of the world.

I would say that the NCI would have a limited ability, on its own authority to have an impact on these ecological consequences, other than to speak, to communicate, to stress the importance of these areas. We also need to make sure that NCI staff are well versed in them and can defend the importance of these areas, and that the countries we collaborate with show an appropriate level of appreciation for those resources in order for us to establish collaborations to begin with. Such countries hold a global treasure in trust.

Mr. PORTER. I was going to say quite the contrary, that people with your kind of credibility and with an interest in the subject that interests most of the human race, if you say this is a problem for the world, people would really listen.

And so I would urge you to be saying that as often as you possibly can, and I assume you do that.

Dr. BRODER. We are very concerned about this issue; and as I mentioned, no scientist whom I respect has taken any position other than that.

AZT

Mr. PORTER. What has been the role of NCI in the development and approval of AZT for AIDS patients?

Dr. BRODER. Sir, the development of AZT, in my opinion, is an outgrowth of the viral cancer program and the developmental therapeutic program of the National Cancer Program, spanning a time going back approximately 25 years.

AZT was synthesized by Jerome Horowitz, who then was working at the Detroit Institute for Cancer Research Foundation, now called the Michigan Cancer Foundation. He synthesized AZT, sometimes called azidothymidine, for the first time in 1964 under an NCI funding instrument that was the equivalent of an R-01 grant. We believe that a number of investigators who are full-time employees of the government or in some cases receive grants-in-aid from the government and from the NCI specifically played a very important role in the collaboration with the Welcome research laboratories to develop AZT.

We believe the government was a full partner in the development of this drug.

Mr. PORTER. Have there been any cooperative agreements between NCI personnel in the commercial sale of AZT?

Dr. BRODER. There are no cooperative agreements that affect or regulate the licensing or commercialization of AZT at this time.

Mr. PORTER. I have a number of other questions that I would like to submit for the record. I know my time is up, but I very much appreciate your answering these, and would ask you to answer some further ones.

Dr. BRODER. Be very pleased to.

Mr. NATCHER. Mr. Hoyer, I yield.

CANCER CENTERS

Mr. **Hoyer**. Thank you very much, Mr. Chairman, Dr. Broder, Dr. Roper, and Dr. Raub.

The question of the cancer centers has been addressed, but I may not have heard the answer. As I understood your answer to Mr. Early's question, you need $144,000,000 extra. How is the $144,000,000 to be used?

Dr. **Broder**. The $144,000,000 represents a figure which was in our Bypass Budget, documented as a professional needs assessment, and the functions of that would be to restore centers that were phased out in 1989 or 1990, or which had downward negotiations against their funding levels.

Mr. **Hoyer**. How many centers were in that category?

Dr. **Broder**. In 1989, we phased out approximately four centers.

Mr. **Hoyer**. Leaving how many?

Dr. **Broder**. We currently have 56 centers in our program.

Mr. **Hoyer**. All right.

Dr. **Broder**. Of which approximately 80 percent are clinical and comprehensive and approximately 20 percent are basic.

Mr. **Hoyer**. Now, would restoring the four also restore full funding to the balance?

Dr. **Broder**. It would fund continuing centers at recommended levels and it would fund approximately five new centers.

One of the areas which is a concern for me personally and many people on our staff is that we need to make sure we have a diversity of centers in our program. We should try insofar as we can, within the peer review process, always adhering to standards of peer review and excellence, to achieve an intellectual diversity and geographical diversity.

I am concerned that some areas of the country, the Midwest and the Southeast, perhaps, are under-served with respect to cancer centers. And therefore, we need to look as carefully as we can within available funds to see what we can do.

The Bypass Budget permits us to do this. We would also fund one or more minority demonstration centers. These would be centers that would be focused on specifically addressing the problems of certain minorities and poor people in under-served populations, including rural populations where certain kinds of cancer are a significant problem.

We would also try to fund supplements focusing on individuals over the age of 65 where our cancer statistics are not good by anybody's standards, to address the special needs of prevention, early diagnosis, and treatment.

And there are special needs of people over 65. Those would be the major focal points.

Mr. **Hoyer**. Let us assume that you don't get the $144,000,000 extra, just for the sake of argument. How is it going to impact on the 56 centers?

Dr. **Broder**. Our current projections are that we will, in fiscal year 1991, either need to phase down three to four centers and/or seriously downward negotiate the recommended levels.

NEW INVESTIGATORS

Mr. HOYER. And Mr. Early pursued the question of downward negotiations as well as the pay lines. Let me switch to that issue.

Doctor is there any correlation between pay line levels and the maintenance of the flow of new researchers into biomedical research?

In other words, at what point do you get your pay lines so low that new researchers make a determination that this is not a field which they are out to enter?

Dr. BRODER. In my professional opinion, we are at that point, although we do have some mechanisms which partly correct this effect, including the First Award system, which is specifically targeted to individuals entering the competition for the first time.

We make special allowances for young men and women or new investigators coming in for the first time, and we try to give every possible break in favor of allowing them to receive funding and to proceed in investigator initiated projects.

But I do think that——

Mr. HOYER. Doctor, may I follow up on that?

Dr. BRODER. Certainly.

Mr. HOYER. That being the case, do you have any evidence that the more experienced researchers are discouraged and leaving basic biomedical research?

You want to encourage new people coming in. That makes sense, unless it mitigates against retaining the more experienced researchers who find that the well is drying up.

Dr. BRODER. I take your point, and I think the overall determinant is the support we can do, there is no way of getting around it, it has to be the available funds. That drives every other consideration.

Mr. HOYER. Doctor, I share Mr. Early's view that one of the problems we have, perhaps as a society, is thinking that way.

The availability of resources should not drive us. The challenge drives us, the need drives us, the necessity. The critical nature of what we confront drives us.

You can obviously take that to an extreme.

I think we are going to the extreme in the other direction. We are the richest nation on the face of God's earth. We have the resources.

Dr. BRODER. Sir.

Mr. HOYER. Period. We have the resources. What drives us is the need.

Doctor, I know that you probably agree with that, and I interject that only because we can get so tied to the problem of available resources that we lose sight of the objectives that we need to obtain as a society.

I interrupted you, and I apologize.

Dr. BRODER. No, I am sorry, I think I interrupted you. I apologize.

I can assure you that the national cancer program has the intellectual wherewithal to comply with the spirit of all of the requirements that we need to do to prevent and cure cancer.

TRAINING OPPORTUNITIES

Mr. HOYER. I think we on this committee are absolutely convinced of that.

Do we have any studies of how we stand with reference to the supply of basic biomedical researchers and investigators?

Dr. BRODER. Yes, we do, and there have been several projections. Some of these have been prepared by the NIH, and some of them have been prepared in particular with the collaboration of the NIGMS.

We could either submit those for the record or perhaps I could yield to Dr. Raub, whatever is your pleasure.

Mr. HOYER. Either way you want to do it.

Dr. RAUB. In terms of the overall studies, the National Academy of Sciences reports on overall opportunities for research training. The latest NAS report entitled "Biomedical and Behavioral Scientists: Their Training and Supply," has just become available within the last few months and will be updated every four years. I am not aware of any major statistical studies on the earlier issue regarding individuals becoming discouraged. However, there are many anecdotes of young investigators who see their mentor, an established scientist, in the laboratory in a state of high anxiety over whether funding will be renewed.

Mr. HOYER. Doctor, do we have any way of identifying those folks who are choosing basic biomedical research over some other discipline?

Dr. RAUB. The best mechanism for us is to look at the individuals who have been part of the formal training programs and track their careers. Some of this is done by interview or other reports.

Mr. HOYER. You might want to expand upon that, either one of you, or four of you, for the record. I think that would be useful.

Thank you, Mr. Chairman.

[The information follows:]

SUPPLY OF BIOMEDICAL RESEARCH INVESTIGATORS

There are several studies, most notably "Science and Engineering Indicators—1989" (National Science Board), that predict a shortfall in scientific, including biomedical scientific, research personnel in the near future. Current indicators suggest that increased efforts are needed to recruit and retain scientists at all stages of the educational process. However, the report that deals most specifically with personnel issues for biomedical research and the National Research Service Award (NRSA) programs administered by the National Institutes of Health (NIH) is "Biomedical and Behavioral Research Scientists: Their Training and Supply", prepared by the Institute of Medicine/National Academy of Sciences. The most recent report in this series was released in January, 1990, and it is planned that the report will be updated every four years. The report provides recommendations for the numbers of trainees and fellows that should be supported by NRSA programs to meet biomedical, behavioral, and clinical research personnel needs of the future. The current status and future need for under-represented racial minorities and women in biomedical research and process components of the NRSA programs are also assessed by the IOM study group.

The labor market assessment model used by the IOM to estimate the number of new researchers needed to meet future personnel demands includes a demographic/economic component that estimates scientist attrition due to death, retirement, outmigration and inmigration. However, mere replacement of scientists who leave biomedical research is not sufficient. A more accurate estimate of need takes into account the increasing demand for scientists in industry, government, and other nonacademic sources that draw on the same pool of trainees. The IOM model accounts for these factors. Therefore the estimates of personnel needs in biomedical research used by NIH are based on both the predicted need to *replace* and the predicted need to *compete for* personnel resources.

The IOM report asserts that the greatest increases in personnel will be needed in the area of basic biomedical research. The attrition of minorities and women in the pipeline is still significant. Both recruitment and retention of these groups is essential to meeting personnel goals of the future.

Several databases in the Division of Research Grants/NIH have information about NRSA grants and trainees and fellows (e.g., IMPAC, Training and Fellowship File). These sources are used by NIH on a continuing basis to monitor the status and efficacy of our programs. The NIH Task Force on Biomedical Research Training used these sources of data to evaluate certain aspects of training. These data-based evaluations were important considerations in the development of the recommendations of the Task Force.

Both the IOM and the Task Force have recommended improvements of data systems for tracking the careers of trainees and fellows. With such improvements we would be better able to determine what aspects of training and the research environment are most important in the process of training skilled, productive, committed biomedical researchers.

PROFESSIONAL JUDGMENT BUDGET

Mr. NATCHER. Dr. Raub, as you know, Dr. Broder has testified that he would need additionally about $700,000,000 for his professional judgment budget. What would be the total for all of the institutes, Dr. Raub?

Dr. RAUB. Our professional judgment budget on behalf of all of the institutes for fiscal year 1991 would be $10.7 billion, Mr. Natcher.

CONSTRUCTION

Mr. NATCHER. Thank you.

Now, Dr. Broder, how much of the $15,000,000 cost for construction grants at NIH will be financed by the Cancer Institute?

Dr. BRODER. As we speak today, in effect, approximately $2,000,000 has been transferred from the NIH to the National Cancer Institute to fund approximately two very high priority construction grants, which were in our system, had had high priority peer review, and had been approved by the National Cancer Advisory Board.

My understanding is that the NIH will be taking care of an RFA to handle other construction grants, and we would expect that some grantees from the National Cancer Institute would apply for that RFA.

Mr. NATCHER. The President's 1991 budget, as you know, does not propose any funds for cancer construction grants, except for maintenance of the Frederick Cancer Research Facility. The head of the Cancer Advisory Board feels strongly that this should be changed.

How do you feel about it, Dr. Broder?

Dr. BRODER. I think that there are very significant construction needs, extramural construction needs in the country.

I feel we have a highly important set of programs, and there are many important projects that deserve our consideration.

REPROGRAMMING

Mr. NATCHER. If you could make a decision to reallocate funds within your current request, how much would you switch to construction?

Dr. BRODER. Sir, are you describing fiscal year 1991?

Mr. NATCHER. Yes.

Dr. BRODER. To make sure that I understand this question, are you saying that the Congress would give us permission to reprogram into a construction line?

Mr. NATCHER. Yes. You are right, Doctor.

Dr. BRODER. Sir, I would prefer that as a discretionary device. We feel we have an authorization for construction, and the NCI should use it, if possible.

At the present time, it would be necessary to balance all of our competing needs, and I would be very happy to submit a figure for the record, but perhaps it's best that I not give you a figure right now.

Mr. NATCHER. Can you give me just some idea of the amount Doctor?

Dr. BRODER. Okay.

I believe that we would be looking at approximately $5 to $10 million as a goal, but that would need to be balanced against a number of competing requirements, and I hope that this is not taken as a promissory note.

[The information follows:]

REPROGRAMMING FOR CONSTRUCTION

Construction is one of the many foundation stones of NCI. It should be funded recognizing the need to develop and maintain a good balance between this area and the many other areas needing attention within the Institute, e.g., research project grants, funding for cancer centers, clinical trials, and cancer prevention and control activities. Should the authority exist to reprogram funds into the construction category, NCI would prefer to reserve any commitment on reprogramming for construction until the total budget level for the Institute is established. Five million dollars would be a rough target figure, but available funds and competing priorities would significantly affect the final figure.

FREDERICK CANCER RESEARCH FACILITY

Mr. NATCHER. I understand.

Doctor, how much are you budgeting for repairs at the Frederick facility?

Dr. BRODER. Approximately $1.5 million.

Mr. NATCHER. Last year, you testified that $3.5 million would be needed each year for repairs at Frederick. Is this still a good figure?

Dr. BRODER. Sir, I believe that that is an approximate figure, and the range should be approximately $3.5 million, perhaps in some years, $5 million.

The Frederick Center now has buildings that are more than 30 years old, and they require a high degree of preventive maintenance for a number of issues, some of them related to biosafety and other things.

Our Frederick operation is an exceedingly important part of our cancer research and AIDS research.

EARLY DETECTION

Mr. NATCHER. Doctor, we have received a number of letters from Members in the House and in the Senate expressing concern about funding for early detection programs, particularly in the area of cervical and breast cancers.

What does your current budget do to address these concerns, Doctor?

Dr. BRODER. Our current budget is approximately $8.6 million for issues related to breast cancer screening; we expect that it will go up to approximately $9,000,000 in fiscal year 1991. For cervical screeing. it is currently $6.2 million and projected to increase to $6.4 million in 1991.

PREVENTION ACTIVITIES

Mr. NATCHER. Overall, the budget request proposes less than 1 percent increase for cancer prevention and control. Again, within the limits of your current request, Doctor, are you satisfied with the amount allocated to prevention activities, 1 percent?

Dr. BRODER. Sir, I believe the prevention activities are an exceedingly high priority and an important cost-effective approach for the entire country.

Prevention and public health initiatives are going to become an important priority for the National Cancer Institute as they have in the past, but perhaps more so.

I believe that we will be significantly challenged at that 1 percent increase.

EARMARKS

Mr. NATCHER. Doctor, as you know, on our subcommittee we have been right successful down through the years by treating everyone fair. We have a request from time to time to earmark money here and to earmark money there.

Some of the Members want the committee to earmark certain amounts for certain cancers or certain prevention initiatives. How do you generally feel about this, Doctor?

Dr. BRODER. Sir, I would like to take this opportunity to express my personal gratitude to you for your career-long stand against earmarks.

Mr. NATCHER. Thank you very much, Doctor. Don't you change that.

Doctor, don't ever change.

Dr. BRODER. Sir, I am not likely to.

PUBLIC HEALTH INITIATIVES

Mr. NATCHER. I appreciate it.

Why hasn't the private sector mounted massive screening programs for these cancers, like those done for tuberculosis in the 1950s and 1960s, Doctor?

Dr. BRODER. I think it is difficult for the private sector as I understand that term to be used to undertake certain types of large-scale public health initiatives.

I think that more properly this would be the function of government at a local, state, and Federal level, and I believe the National Cancer Institute certainly has a role in these prevention and screening activities, particularly to define the scholarly basis for the science behind new screening, especially what is the proper implementation, and how to implement new ideas in the communities.

And once that knowledge base is obtained, once we have the knowledge base of how to go about something, establish the know-how—and that includes defining what works in a community—then I think other agencies of government can have a significant role.

But our job is to define what works and how to make it work. And that is not always intuitively obvious. What works in an urban center may not work in a rural setting. What works in one cultural context may not in another.

Our job is to find out what works, prove it, develop an evaluation phase, show that we have done our job or not, and then turn it over to other agencies of government which are more properly suited for that function.

Mr. NATCHER. Thank you, Dr. Broder.

Mr. Conte, I yield.

POLYMERASE CHAIN REACTION

Mr. CONTE. Thank you, Mr. Chairman.

Dr. Broder, I want to welcome you to our hearings today. We have witnessed tremendous progress accomplished by your fine scientists and directions in the past year, and I want to do all I can to help keep the momentum going for the coming decades so that we can find a cure for cancer.

Mr. Chairman, last week you said you were looking for someone at NIH that could take the place of Gorbachev, the picture as Time's Man of the Year on the cover; the Man of the Decade, I should say.

Well, I found your man, or should I say I found your molecule. Science Magazine has called a compound involved in the PCR reaction as its 1989 Molecule of the Year.

Mr. NATCHER. All right. Thank you.

Mr. CONTE. PCR is a revolutionary tool that NIH scientists are using right now, to produce better diagnostic tests and generate quicker and more accurate results in the research of dozens of diseases.

Dr. Raub or Dr. Broder, could you share with us how PCR might be used in future research and why it's such an important development in biomedical research?

Dr. BRODER. Sir, I would be pleased to. PCR—polymerase chain reaction—is an important revolutionary tool which has emerged primarily through the actions and research activities of certain private sector biotechnology companies, which in turn derived much of their know-how and much of the overall basic science approaches from work supported and promoted by the National Cancer Program.

PCR, in brief, allows the amplification, the expansion of very tiny amounts of DNA, which is the essence of life and is the genetic material that determines the code of every cell in a human being.

In effect, by analogy, what it allows us to do is take a whisper of a sound and fill the room with the volume of information. What you can do with PCR is take an exceedingly tiny, infinitesimal strand of DNA and actually expand it so that it becomes easily detectable, so that you can work with it, so that you can sequence it. And it allows approaches that were never possible before.

PCR has affected science from A to Z. It has affected the archaeologic and anthropological research that the world can now do. It's possible to determine the genes of mummified human tissues. It's possible to map the genes of extinct animals. It's possible now to have new forensic applications. For certain types of criminal activities, new kinds of evidence can be brought to bear.

With respect to biological science, PCR is capable of determining small amounts of residual genetic information inside cells. It allows the detection of the AIDS virus in a way that would have never been possible before. It allows the detection, at least on an experimental basis, of the resistance of certain AIDS viruses to AZT even before certain things have happened at a clinical level.

GENE CLONING

In the realm of cancer, PCR has allowed a significant expansion of our ability to clone and sequence genes. PCR allows us the ability to detect small abnormalities in what are called oncogenes, by expanding certain break points or genes under study.

PCR has permitted new ways of deciding what a cell is choosing to express because one modified version of PCR actually starts with RNA, which is the transcript of a DNA molecule.

And then it allows us, in a sophisticated pace, to amplify DNA starting with the RNA transcript. It would be analogous to taking the transcript of this proceeding to actually recreate the voice of a Member of this committee.

This may not be exactly the correct metaphor, but the concept is not that far off.

So this technology is able to have an effect on a broad front in cancer and AIDS and in unprecedented ways that go beyond the confines of the usual things we discuss here.

Mr. **Conte**. How about Lyme disease? You mentioned AIDS, cancer.

Dr. **Broder**. Sir, you could also apply it and it has been applied as a diagnostic technology because it detects pathogens in a reliable way and can be set up in such a way that it won't detect normal tissues if done correctly. It can work in Lyme Disease.

This gets back to the question asked earlier, however. PCR is only as good as the people who do it, and if you don't know what you are doing, you will get an answer which is also of no relevance and not useful.

But assuming a high level of expertise, the technique can be applied in a number of ways. I think it's truly a technique that has overtaken a number of fields in ways that I don't think anybody predicted even five or 10 years ago.

PROSTATE CANCER

Mr. **Conte**. Dr. Broder, prostate cancer is a common disease among older men. Now I hear a new drug and I read about a new drug being tested at NCI, Suramin, which may be helpful in prostate cancer in spreading to the bone.

Can you tell us about the potential of Suramin?

Dr. **Broder**. Sir, prostate cancer affects approximately 106,000 Americans each year, one-third of whom ultimately succumb to their disease.

It's a high priority item for the National Cancer Institute. Among the many research and development activities is our search for new drugs. In the past year, combinations of Flutamide and Leuprolide have become available and are being used, and this is in part a reflection of activities of the National Cancer Institute.

The drug Suramin which is an offshoot of our AIDS research activities has been found to cause regression in some patients with advanced metastatic prostate cancer. It can relieve bone pain, and restore functional activity to certain patients.

The overall activity and safety are undergoing tests, but we believe it's a significant, but not curative, addition to armamentarium against prostate cancer and will be one new tool that we will use.

We hope that we can incorporate it into early treatment. In my opinion, the ultimate value of the drug will be in combinations, not to rely on Suramin alone but to bring in Suramin along with other types of therapies, perhaps adding it in certain early stages where radiotherapy or surgery is being used as an additional approach.

And this would be the kind of thing that we are doing.

Mr. **Conte**. Are there any other drugs which may help the patients with metastatic prostate cancer?

Dr. **Broder**. The regimen of Flutamide and Leuprolide can provide palliation to certain patients and can prolong survival of certain patients with prostate cancers.

All of the other drugs are in stages or approaches that would be considered experimental and it would not be possible to say that they have had a proven role.

Mr. **Conte**. How about leuprin?

Dr. **Broder**. That is in the category of drugs that we were talking about.

There are a number of anti-androgenic drugs which would be used in both the clinical and experimental setting because the prostate is quite sensitive to certain androgenic stimuli.

I believe, however, we need to do more in the way of finding out what causes prostate cancer to begin with. We need to develop new research approaches to prevent the disease and possibly how to detect it early where early treatment might make a difference, and a great deal of our activities will be focused in this regard.

There is still a great deal of uncertainty about two technologies. One is called ultrasound, and one is called prostate specific antigen—PSA. Ultrasound is a way of sending sound signals into the prostate gland and getting images, PSA is a way of testing the blood stream to see if there is a prostate cancer in an early stage.

Both of those, in my opinion, remain unproven technologies, interesting, but unproven; and one of the functions that we are going to do is to actually nail down how they can be used appropriately for the trials so that we can respond as to whether these technologies can make a difference in prostate cancer.

GENE TRANSFER THERAPY

Mr. **Conte**. Now that the biosafety committee at NIH gave the go ahead for genetic therapy for ADA deficiency, there is much promise for the treatment of other diseases as well.

I know there is a long way to go before genetic therapy becomes established, but the development of gene therapy is one of the most promising, exciting frontiers in all of medicine in the coming decade.

Can you explain to us in simple terms how does genetic therapy work?

Dr. **Broder**. Sir, I would be pleased to. In effect, genetic therapy, as you are using the term, refers to a methodology for inserting a foreign gene into a human cell by any of several possible technologies, and then establishing a therapeutic regimen so that the foreign gene expresses itself in a human being for the purpose of correcting a metabolic or biochemical or immunologic problem associated with that person.

It could be used in certain areas of cancer research. It could be used to correct some immunodeficiency disease disorders. For example, there is an immunodeficiency disorder of children which is devastating in its consequences, which is catastrophic and lethal, which involves the inherited loss of an enzyme called adenosine deaminase—ADA.

In brief, this enzyme detoxifies the build-up of purine-like molecules. In the absence of this enzyme, there is a toxic metabolic waste syndrome inside cells of the immune system and they die.

In consequence thereof, the child born with this defect in effect has the functional equivalent of the acquired immuno-deficiency syndrome that we see in adults, and even on a worse scale.

It's possible to provide this enzyme in several formats to restore the detoxifying capacity that is lost as a part of an inherited abnormality.

And scientists from the NCI working together with their colleagues at the National Heart, Lung, and Blood Institute are currently proposing to insert the gene adenosine deaminase into the T cells, the immune cell which is destroyed in the kind of disease that we are talking about. The disease goes by the name of severe combined immuno-deficiency. We hope to re-implant these cells, appropriately expanded, into children who are deficient of the enzyme.

Although I cannot give you a promise, we expect that we will go through the various regulatory hurdles that are necessary—and they are formidable—and if we successfully complete them, it's possible that by September or perhaps in the fall of this year we would start those experiments.

But this last year, we crossed the Rubicon. There is no going back. Genetic therapy is here, and the foundation stones that have been laid for this approach will stand.

GENE TRANSFER THERAPY AND CANCER TREATMENT

Mr. **Conte**. What types of cancer can be treated through genetic therapy?

Dr. BRODER. Well, there are theoretical approaches that could conceivably involve genetic therapy, but they are not proven, and they are basically on the drawing board.

But the theory would be that it's possible that if certain cancers are caused by oncogenes, which are genes that are abnormally activated and cause the transformed state or suppressor genes, a kind of regulatory gene, that it might be possible to actually develop a system that replaces those genes in certain cells and allows a reestablishment of a normal growth pattern. This is a projection, a theoretical idea. And it's not proven.

It may also be possible to insert certain genes into the bone marrow of a cancer patient, not into the cancer cells but into bone marrow precursor cells to render them impervious to the effects of cytotoxic drugs that might be necessary to treat the cancer. This could shift the balance in favor of the patient by making the bone marrow resistant to some of these drugs and thereby allow a higher intensity of chemotherapy, because we frequently have situations where a cancer is responding but the patient's bone marrow is destroyed, and we cannot administer an effective drug any more.

So those are a few of the ideas that I can discuss with you and be happy to keep you informed as these projects evolve.

Mr. CONTE. I appreciate that.

Dr. BRODER. But we are still at an early phase for that.

PEDIATRIC AIDS

Mr. CONTE. NCI, in cooperation with NIAID, is playing a significant role in the AIDS research and particularly in pediatric AIDS and the impact on children.

Can you share with us what existing leads are there in the pediatric AIDS?

Dr. BRODER. Yes, I can.

Pediatric AIDS is a growing part of the entire AIDS epidemic, and in some ways is a very rapidly growing part. Our program early on committed itself to addressing the problem of AIDS in children and particularly with respect to the implementation of new therapeutic agents in children.

Most of this work is being done intramurally by Dr. Phil Pizzo, who is the head of our Pediatric Oncology Branch. He works very closely with investigators in the National Institute of Allergy and Infectious Diseases with an exchange of information and exchange of ideas and exchange of resources.

He has pioneered the implementation of anti-retroviral therapy, taking drugs alone or in combination and intervening in children against the AIDS virus.

Many of these children have dementias and essentially a kind of loss of intellectual functioning, a regression of milestones of growth.

Some of the drugs alone or in combination have reversed these dementias and loss of intellectual functions, and we feel that this is a major step and is one of the few times that a chronic and infectious dementia can be reversed by therapy.

This is one step. Dr. Pizzo is also working on protocols which may lay the foundation stones for preventing maternal to fetal transmission of the AIDS virus. We think this is a growing problem.

One of the reasons why children get AIDS is because they acquire it in utero from an infected mother, and we are exploring in Dr. Pizzo's program, the possibility of administering certain drugs or new molecules called CD-4 or a version of CD-4 which can be adapted for this use to block this transmittal step in utero.

I think I have keyed in on some of the issues that he has studied.

Mr. CONTE. Thank you, Doctor.

I have many, many more questions. Unfortunately I have exhausted my time.

[Discussion off the record.]

Mr. NATCHER. Mr. Early, I believe you have another one.

DOWNWARD NEGOTIATIONS OF GRANTS

Mr. EARLY. Doctor, Mr. Myers commented and asked about the mammogram. You responded and then, with Mr. Conte, you elaborated that it doesn't do any good to have a mammogram if there isn't follow up with professionals.

Would that be an analogy of the institutes, the scientists, the MDs, and all professionals who put together a budget, and then OMB tells you where to cut it?

I mean, should an accountant tell you what the best science is? You don't have to answer that, Doctor.

I want to ask, about some current competing and non-competing grants; they are not from my state. In 1990 one grant was going to be funded at $142,000, and the investigator involved in this grant told me, he might as well leave. As far as you know, you are taking it away. More is needed for salaries, and all the equipment and supplies and other and then there is downward negotiation. The grant is going to be $123,000. And I am sure a lot of people will say, well, let him leave.

We cannot take that attitude, Doctor. But isn't an investigator in that situation going to have a tough time producing anything rather than just surviving?

Dr. BRODER. I think it's possible to downward negotiate to the point that you depreciate the ability of the grant to do its job. I definitely believe that can happen.

Mr. EARLY. And I think it's happening, Doctor.

Another is a program project grant that was recommended at $899,000 for 1990. It's going to be funded at $804,000. These are actual grants, Doctor. We have to come to grips with this irresponsible downward negotiation and at least say what we are funding and what we are not funding. All the money should not be going to defense and to these other groups.

The other one is a core grant which, in this year, should be funded at $4,000,967; it's ongoing to get $4,000,000. Wouldn't you say, Doctor, that all those downward negotiations are a threat to good science?

Dr. BRODER. I think downward negotiations nullify peer recommended funding. I believe in peer recommended funding. I think downward negotiations are one of the necessary choices which comes into play when available funds are not able to stretch to meet everything.

Mr. **Early**. Well, that is necessary only because your backing into an amount, and not because of anything to do with science, isn't it?

I mean, it's just necessary because of the available funds.

Dr. **Broder**. We have many scientific opportunities in the National Cancer Program.

Mr. **Early**. Thank you, Mr. Chairman.

Mr. **Natcher**. Mr. Conte, I believe you have a question.

RISK FACTORS FOR BREAST CANCER

Mr. **Conte**. Just a couple here, Mr. Chairman. Thank you.

As you well know, Dr. Broder, the more effective treatment of breast cancer is early detection. I hear that your breast cancer detection demonstration project has come up with a formula that can calculate a woman's risk of developing breast cancer within the next 10 to 30 years.

How does this formula work?

Dr. **Broder**. Well, basically statisticians and medical oncologists are able to assess a number of risk factors that are known from epidemiologic studies. Some of these risk factors relate to what was the age of a woman's first menstruation.

Some of the risk factors relate to when a woman had her first full-term delivery. Some of the risk factors may relate to whether a woman has had a strong family history of breast cancer because strong family histories do represent one risk factor, and so on.

There are a series of other factors that are brought into play, and then a statistical projection can be put in, a kind of odds ratio can be put in to describe what is the probability of a woman acquiring breast cancer within a 10 to 20 year period of time.

I would like to say while this is an important exercise, and it's something that can be done, I think it has to be viewed in a certain context. It's particularly useful for statistical stratification of a clinical trial.

That is, if you are going to do a clinical trial and you want to make sure you have a level playing field to all people that enter a study and that you are not going to get the wrong answer by thinking something works when really—you accidently put people who have a better prognosis in a certain category, this kind of work is very important.

In general terms for a physician to counsel women as to the kinds of plans for follow up and that an individual woman might need, I think it's also appropriate.

But I think you can carry these types of numbers too far, and I think doctors should use a certain amount of humility as to what they can and cannot predict.

Mr. **Conte**. I will have follow-ups on that, and you can get them for the record.

What are the limitations of the model? And if this formula holds up, what are the diagnostic and clinical implications from patients and doctors, and what else is NCI doing on full blown detection of breast cancer. And you can get those all for the record.

[The information follows:]

EFFORTS IN EARLY DIAGNOSIS AND SCREENING FOR BREAST CANCER

Development of breast screening plan. In cooperation with the Centers for Disease Control and the Food and Drug Administration, NCI staff are developing a national plan directed at increasing breast and cervical cancer screening among women with the ultimate aim of reducing cancer mortality. This project is now in the planning stage, but we hope a coordinated national effort will produce rapid change in screening.

Communications. NCI is working to get the message out that use of screening mammography can lower breast cancer mortality. NCI's Office of Cancer Communications is sponsoring a Breast Cancer Awareness Program which is being popularized through the mass media.

Health promotion. In partnership with the American Cancer Society and linked to professional medical organizations, NCI is encouraging physicians to screen all eligible women for various cancers including breast cancer. A new brochure on the Working Guidelines for Early Cancer Detection is being developed to be mailed to all physicians.

Data Analysis. Analysis of national data on barriers to breast cancer screening are in progress in order to better design intervention programs. One key message is education: women are generally not aware that breast screening should occur in the absence of symptoms.

Technological improvements for improved quality and increased screening capacity. At present, one of the limitations to more widespread use of mammography is volume and cost. There is an urgent need to develop a digitized mammogram that is as accurate as our present low dose film screen mammogram. This would permit much more efficient use of a single machine, allowing hundreds of mammograms to be performed per day as compared to the current maximum of 40 per day. It would also greatly enhance the ability of mobile units to take mammography to convenient locations.

Analysis of mammography supply: NCI and FDA staff have jointly analyzed data on the supply of new dedicated mammography machines. Findings on the supply and distribution of machines demonstrate that the U.S. is well supplied with this technology.

International breast cancer screening database: In collaboration with investigators from other developed countries, the NCI is creating an international database on breast screening. It is hoped that the organization and performance of breast screening in other countries can provide models for the U.S. health care system as the use of breast cancer screening increases.

Other early diagnosis and screening for breast cancer initiatives include: A cooperative network of community intervention studies is underway in seven states to improve the utilization of mammography, breast exams, and breast self examination: California, Massachusetts, New Jersey, New York, North Carolina, Pennsylvania, and Washington. To date, the baseline studies point out marked differences in perceptions in barriers to using mammography for women when compared with their physicians. Women most often report a lack of a problem, having given little thought to mammography, or no physician referral as reasons for not having a mammogram. In contrast, the community physicians report that cost, inadequate insurance coverage, and equivocal radiology reports are barriers to mammography referral. These results were presented at the 1989 American Public Health Association meetings in Chicago. Interventions are underway to remove these barriers and increase screening rates in each community.

A second mammography initiative is a joint NCI-National Institute on Aging-Health Care Finance Administration project to supplement grants which promote breast cancer screening in older women and/or evaluate various effects of insurance coverage on costs, stage of cancer, and barriers to mammography in these areas. Four of the six NCI Mammography Consortium grants have been supplemented to promote or evaluate breast cancer screening in older women over the next two to four years. A conference on implementing mammography screening guidelines for women over the age of 75 has been organized by NCI, the National Institute on Aging, and the University of Massachusetts. The conference will be held July 30-August 2, 1990.

The worksite offers a unique opportunity for long term and repeated interventions with a sizeable and stable adult population, and it allows both occupational exposures and lifestyle factors to be addressed in an integrated fashion. NCI has recently funded one grant to design and evaluate breast cancer screening programs at the worksite. The intervention project is based in Florida, and began its four-year project in October, 1989.

Physicians are also an important intervention channel for breast cancer screening activities. NCI sponsored research has demonstrated that primary care physicians can effectively deliver cancer prevention services. Recent work indicates that cancer prevention services are not routinely delivered in primary care practice. NCI is funding four research grants to identify effective methods for improving cancer prevention within primary care practices. Two of these projects have recently shown the positive effects of office-based cancer screening reminder systems on increasing breast cancer screening tests. These results were presented at the 1989 American Public Health Association meeting in Chicago.

Recently a Request for Applications on "Public Health Approaches to Breast and Cervix Screening" was released and competed. It will demonstrate how a consortium of community agencies can develop and evaluate strategies to increase the availability, accessibility, awareness, and utilization of breast cancer screening regimens including mammography, clinical breast examination, and breast self-examination among low income, low education level, and minority women over 40 years of age. The grants are expected to be funded by July, 1990.

There are currently four funded grants related to Technical Capacity Building in Health Departments whose purpose is to build public health department capacity to provide cancer prevention and detection services. Each of the following grantees is trying to increase mammography-related policies and services in their health area:

- Supported in part by an NCI Technical Capacity Building Grant, the health department in the State of Michigan used an extensive task force and peer review procedure to prepare and promulgated guidelines for the conduct of breast cancer screening. The guidelines cover the roles of primary care physicians, radiologists, surgeons, pathologists, radiology technicians, safety and quality assurance.

- The health department of Los Angeles County is pilot testing a screening mammography program for its own employees age 50 and above with the ultimate objective of having those employees sensitize and recruit patients for mammography.

- The State of Connecticut health department utilized focus groups and other marketing techniques to modify its breast screening programs.

- Supported by NCI and CDC, the Colorado Health Department is following women screened in the American Cancer Society-sponsored reduced cost mammography program. A test of three different reminder letters for screening in subsequent years to women whose mammograms were normal is in progress.

The Data-based Intervention Research Project currently funds five grants located in Illinois, Nebraska, North Carolina, New York, and Texas which involve low-cost mammography screening and related education in counties with high-risk populations within each of these states.

The Avoidable Mortality from Cancer in Black Populations initiative contains three contracts which promote the use of breast cancer screening in the following areas:

- Chicago, Illinois -- Efforts to increase rate of breast and cervical screening in central city locations for Black females 21 and older are supported.

- Detroit, Michigan -- Use of a physician prompt system to increase the rate of mammography by Black females 40 and older is underway in inner city Detroit.

- Atlanta, Georgia -- Use of lay health workers to increase knowledge, change attitudes, and modify practices to increase breast cancer screening in Black females 21 and older is being supported in inner city Atlanta.

Another grant project recently funded in New York focuses on emergency room cancer screening by providing breast cancer screening services to Black females patients and/or female companions of patients while waiting for services in hospital emergency rooms.

CATHEPSIN-D

Mr. **Conte**. While we are on the subject, I hear that a newly discovered protein, Cathepsin-D, which is secreted by breast cancer cells, can indicate whether a woman might have a recurrence of a surgery.

What are the prospects of using this protein in the clinical management of a breast cancer patient?

Dr. **Broder**. Cathepsin-D is a kind of special enzyme. It destroys certain types of peptide bonds. It destroys protein-like substances. It may actually be produced or leaked by certain types of cancer cells.

There are data from several groups, including a group in Texas, which have suggested that Cathepsin-D as a marker can be used to predict the probability of whether a woman is likely to relapse, to have her cancer come back following the primary operation to remove the tumor.

This is particularly important because we know that if a woman's lymph nodes are negative—the lymph nodes are the draining portion of her underarm—the odds of the cancer coming back are lessened, but not down to zero.

What happens is, she has about a 30 percent chance of still having a cancer come back. Even though most of the time it won't, 30 percent is still a significant probability.

In that setting, we would like to be able to identify what kind of woman, what category of patient is likely to have a relapse, to target and be more effective and provide cost-effective therapy.

This test is not proven. We will have confirmatory trials in our cancer therapy evaluation program. It's not the only prognostic program that we are studying. There are others.

There is a lot of other research in this area, and it may be possible to develop a profile of substances or prognostic markers.

I think it's better not to put all of our eggs in one basket.

Mr. **Conte**. Thank you, Mr. Chairman.

Thank you, Doctor.

Mr. **Natcher**. Dr. Broder, this has been a good hearing. I want you and your associates to know that you have made a good presentation, all of you.

Dr. Raub, it's been a good hearing. We appreciate it.

Dr. Broder, we want to wish you the best of everything with your assignment. We believe we are in good hands, Doctor.

Thank you very much.

Dr. **Broder**. Thank you, sir.

Mr. **Natcher**. We take up next National Heart, Lung, and Blood Institute.

At this time, we will recess.

[Recess.]

[The following questions were submitted to be answered for the record and the justifications follow:]

CANCER CENTERS

Mr. Natcher. Last year when you presented a similar request, you testified that it would be better to cut back on the number of centers and more adequately fund the survivors. If additional funds are not made available, would we be better off with fewer centers?

Dr. Broder. Members of our advisory boards and representatives from the cancer centers community have advised us that we should, as much as possible, avoid downward negotiations, recognizing that this position may mean the loss of centers. I agree with this position, even though I certainly do not want to lose centers. But, I recognize that reductions below a certain point threatens the excellence of the individual centers and the total portfolio.

Mr. Natcher. How many centers will come up for renewal in 1990 and 1991?

Dr. Broder. Eighteen centers will recompete in 1990 and 10 will recompete in 1991.

EXTRAMURAL CONSTRUCTION

Mr. Natcher. How much of the $15 million cost for construction grants at the NIH will be financed by the Cancer Institute?

Dr. Broder. In FY 1990, NCI was assessed $3.5 million towards the $15 million extramural construction pool currently contained in the NIH 1990 appropriation.

Mr. Natcher. How much of the $15 million is expected to be used for cancer related projects?

Dr. Broder. We have been provided $2 million of the $15 million to support two construction grants with the best priority scores. In addition, our understanding is that NIH is issuing a request for applications (RFA) in the amount of $2.8 million for extramural construction. Cancer construction grants can apply against that RFA and may receive additional funding from that source.

CANCER RESEARCH SUPPORTED BY PRIVATE SECTOR

Mr. Natcher. How much money is the private sector expected to put into cancer research in 1990 and how has this changed in recent years. I am interested both in philanthropic funds as well as private commercial investment.

Dr. Broder. We do not have exact information relative to what the private sector is expending on cancer research. The last data that was available for total funds directed into cancer research indicated that the funding by the Congress for the Cancer Institute represented approximately one-half of the total resources. Included within this estimate was funding from other

Federal, state and local governments plus private organizations such as the American Cancer Society and the Leukemia Foundation.

Mr. Natcher. How much will the Cancer Institute receive this year from private sources and how will this money be spent?

Dr. Broder. This year is a unique year for the National Cancer Institute in terms of funds other than those appropriated by the Congress. Historically, the Institute receives approximately $200,000 a year through contributions by the private sector. The contribution is generally in memory of a family member or friend. These funds are expended under the same procurement guidelines as appropriated funds and have included the purchase of scientific equipment or clinical equipment, patient care activities as well as support for specific scientific areas, e.g., breast cancer activities conducted on campus.

In addition, for 1990 several unique contributions have occurred. Several years ago, the NCI was notified that it was one of several individuals/organizations named in the estate settlement of an individual. Just last month the Institute received $4.1 million as a one-time settlement of its portion of the estate. Also in 1990, another large singular donation was contributed totalling $1.1 million for the Institute to use on lymphoma research.

Through the private fund raising activities of Dr. Armand Hammer, who initiated a campaign called STOP CANCER, substantial funds for cancer research have been raised. To date, the first contribution, almost $3 million, has been received by the Institute. It will be expended for peer-reviewed activities of the Institute. These funds have been allocated to activities such as adoptive immunotherapy projects, epidemiological studies in minorities, research into tumor suppressor genes and clinical trials involving melanoma/ cisplatinum and monoclonal antibodies.

In summary, contributions received for 1990 to the Gift Fund are unique. They are, by far, the largest amount received in any fiscal year and will be used in accordance with Federal guidelines and regulations.

Mr. Natcher. Can you tell us how much money has been raised by the STOP CANCER program to date and how much more is expected in 1990?

Dr. Broder. The National Cancer Institute has received $2.9 million in funds from STOP CANCER. We have been advised that additional funds might be provided in 1990 but it is unknown as to how much will be released to the Institute.

Mr. Natcher. Does the NCI endorse in any way this STOP CANCER fund raising effort?

Dr. Broder. Specifically regarding the STOP CANCER fund raising effort, the NCI responded to this campaign as it would to any potential donor, that the Institute has the authority to accept donations in support of its mission.

Mr. Natcher. Are the gifts to the Institute from STOP CANCER unrestricted contributions available for whatever purposes you see as the highest priorities?

Dr. Broder. The monies received from STOP CANCER will be used, as indicated in last year's Senate Report on the appropriation, to support cancer biology and adoptive cellular therapy as determined by the Director, NCI.

AUTHORIZATION

Mr. Natcher. How many of your current activities are not authorized for 1991 and how much is budgeted in 1990 and 1991 for each?

Dr. Broder. The following NCI activities are to be reauthorized for FY 1991:

- Cancer Prevention and Control, for which $74,944,000 is estimated in FY 1990 and $75,459,000 in FY 1991;

- Construction, for which $5,006,000 is estimated in FY 1990 and $1,479,000 in FY 1991; and

- Training, i.e., National Research Service Awards, for which $35,793,000 is estimated in FY 1990 and $35,793,000 in FY 1991.

1989 TAPS

Mr. Natcher. Insert in the record at this point a list of all taps which have been taken out of the original 1990 conference agreement for NCI.

Dr. Broder. The taps that were taken out of NCI's FY 1990 conference agreement of $1.644 billion follow: Gramm/Rudman/Hollings Sequester, $22.8 million; Procurement Reform, $1.3 million; Extramural Salary Cap, $2.3 million; Department of Health and Human Services Salary and Expenses reduction, $3.2 million; and an assessment for the new Agency on Health Care Policy and Research, $6.0 million. The latter item is contained within our budget but has been earmarked from the NCI share of PHS one percent evaluation funds (authorized by Title XXVI of the PHS Act) for the purpose identified. In addition, NCI was assessed $3.5 million as our share of the $15 million NIH pool for construction. To date $2 million has been approved for NCI construction projects. In total, NCI was assessed approximately $36 million.

UNFUNDED CONSTRUCTION PROJECTS

Mr. Natcher. Submit to the Committee separately, if you will, a list of all currently approved but unfunded construction projects and please update us regularly of any significant additions or deletions as a result of new competitions, funding out of any source or withdrawals.

Dr. Broder. The listing of currently approved construction projects for FY 1990 is reflected below:

Currently Approved but Unfunded Construction Applications:
(dollars in millions)

Institution	Recommended Grant Award (NCI $)
University of Colorado Health Science Center	$2.9
University of Pittsburgh	0.9
Fred Hutchinson Cancer Research Center	3.1
M.I.T. Center for Cancer Research	0.2
	$7.1

Currently Approved and Being Funded Construction Applications:

Institution	Recommended Grant Award (NCI $)
University of Southern California	$1.2
University of Wisconsin	0.4
	$1.6

In addition, it is anticipated that many construction applications will be received by NIH in response to their Request for Applications (RFA) for construction proposals. The application deadline is May 7, 1990. It is anticipated that many of the applications will be from institutions with cancer research centers. As you request, we will provide updated information on this question.

BUDGET REDUCTIONS

Mr. Natcher. Your budget seems to be pretty much a status quo request. Are there any significant reductions which are likely to cause controversy such as the cancellation of major trials, termination of major contracts, or others not previously discussed?

Dr. Broder. This budget request contains adequate funding to maintain momentum in all our high-priority programs, both for cancer and for AIDS research. There will be no terminations of ongoing clinical trials or major contracts due to budgetary restrictions. We will continue to periodically review all our research programs, so that through careful management of NCI's resources, we will be able to redirect funds to high priority areas without precipitating funding crises in other research programs.

PERSONAL SERVICES COSTS

Mr. Natcher. The 1991 budget proposes a 30 percent increase in "special personal services" payments. These costs increase by over $3 million. What is the justification for this change?

Dr. Broder. This category of expenses refers to salary payments made to scientists who are employed at NCI through the use of special (non-civil service or commissioned corps) appointment mechanisms. These temporary scientific personnel bring a variety of needed talent and scientific viewpoints to the Institute; many are foreign scientists. In addition to providing for cost-of-living adjustments for these researchers, the 1991 budget contains adequate funds to allow for an increase in the number of scientists in this special appointment category, including the foreign visiting scientists. Because of the recent changes in East-West relations, NCI anticipates that the collaborations and scientist exchanges with eastern European nations and the Soviet Union will continue to broaden in scope and duration.

TOP RECIPIENTS OF NCI FUNDS

Mr. Natcher. Insert in the record at this point a table showing the top 20 institutional recipients of NCI funding and how this has changed from five to 10 years ago.

Dr. Broder. The lists follow:

Twenty Institutions Receiving the Highest Amount of Support from the National Cancer Institute in 1980

(Dollars in Millions)

INSTITUTION	GRANT	CON-TRACT	CON-STRUC-TION	TOTAL	STATE
University of California	$33.1	$4.0	$1.0	$38.1	California
University of Texas System	23.1	4.5	0.0	27.6	Texas
Sloan-Kettering Institute	20.8	1.9	0.0	22.7	New York
Johns Hopkins University	13.5	1.8	2.9	18.2	Maryland
Fred Hutchinson Cancer Research Center	10.5	1.7	4.6	16.8	Washington
Dana-Farber Cancer Institute	13.6	0.6	0.0	14.2	Massachusetts
University of Wisconsin System	13.0	1.3	0.0	14.3	Wisconsin
New York State Department of Health	11.7	0.9	0.6	13.2	New york
Yale University	11.9	1.6	0.0	13.5	Connecticut
University of Southern California	9.3	2.1	0.0	11.4	California
Harvard University	9.2	0.6	0.1	9.9	Massachusetts
Columbia University	8.7	1.0	0.0	9.7	New York
Michigan Cancer Foundation	3.3	5.9	0.3	9.5	Michigan
Stanford University	8.3	0.6	0.0	8.9	California
University of Chicago	8.0	0.8	0.0	8.8	Illinois
University of Alabama System	7.6	0.2	0.0	7.8	Alabama
University of Minnesota	6.2	1.7	0.2	8.1	Minnesota
Duke University	7.0	1.0	0.0	8.0	North Carolina
Battelle Memorial Institute	1.4	6.1	0.0	7.5	Ohio
Yeshiva University	7.5	0.0	0.0	7.5	New York

Twenty Institutions Receiving the Highest Amount of Support from the National Cancer Institute in 1985

(Dollars in Millions)

INSTITUTION	GRANT	CONTRACT	CONSTRUCTION	TOTAL	STATE
University of California	$54.2	$2.3	$0.0	$56.5	California
Memorial Sloan-Kettering Cancer Center	31.7	2.2	0.0	33.9	New York
University of Texas System	28.4	2.8	0.0	31.2	Texas
Program Resources, Inc.	0.0	24.9	0.0	24.9	Maryland
Dana-Farber Cancer Institute	20.1	0.4	0.0	20.5	Massachusetts
Johns Hopkins University	18.4	0.7	0.0	19.1	Maryland
Fred Hutchinson Cancer Research Center	16.7	1.4	0.0	18.1	Washington
New York State Department of Health	16.1	1.6	0.0	17.7	New York
University of Wisconsin System	14.8	1.9	0.0	16.7	Wisconsin
University of Southern California	14.9	1.2	0.0	16.1	California
Yale University	14.4	1.1	0.0	15.5	Connecticut
Stanford University	13.6	0.1	0.0	13.7	California
Columbia University	13.1	0.0	0.0	13.1	New York
Harvard University	12.0	0.5	0.0	12.5	Massachusetts
Duke University	11.7	0.3	0.0	12.0	North Carolina
Litton Industries	0.0	11.8	0.0	11.8	California
University of Pennsylvania	9.0	0.3	2.5	11.8	Pennsylvania
University of Rochester	10.3	0.0	0.9	11.2	New York
Massachusetts Institute of Technology	10.4	0.1	0.0	10.5	Massachusetts
University of Chicago	10.4	0.1	0.0	10.5	Illinois

BREAST CANCER

Mr. Conte. While we are on the subject, I hear that a newly discovered protein, cathepsin D, which is secreted by breast cancer cells can indicate whether a woman might have a recurrence after surgery. What are the prospects of using this protein in the clinical management of breast cancer patients?

Dr. Broder. Cathepsin D is an enzyme which can digest proteins. It was recently shown by groups in Denmark, France and the U.S. to have prognostic potential in node-negative breast cancer patients. When first identified, cathepsin D showed that it might be an independent prognostic indicator, both in premenopausal and postmenopausal women. A second group independently came to similar conclusions, even though it suggested that cathepsin D appeared to have prognostic value only in node-negative breast cancer patients. This could be very helpful in deciding whether to place node-negative breast cancer patients on adjuvant therapy, since only 30 percent of these patients have recurrence of disease; the other 70 percent could thus be spared the trauma of additional therapy. In the recently published paper, cathepsin D did not add prognostic information about patients with breast cancer which has extended to the regional axillary lymph nodes.

Mr. Conte. Could it guide decision-making in choosing chemotherapy or radiation?

Dr. Broder. Unfortunately cathepsin D does not uniformly predict which patients will develop metastatic disease and which will not. Thus, although it may add some precision in evaluating prognosis, decisions relative to treatment remains imprecise.

Mr. Conte. As you well know, Dr. Broder, the key to more effective treatment of breast cancer is early detection. I hear that your Breast Cancer Detection Demonstration Project has come up with a formula that can calculate a woman's risk of developing breast cancer within the next 10 to 30 years. How does this formula work?

Dr. Broder. It is true that a group of biostatisticians and epidemiologists from the National Cancer Institute used data from the Breast Cancer Detection and Demonstration Project (BCDDP) and subsequent followup studies to develop the prediction formula that you describe.

This formula uses an individual woman's age and status concerning four important risk factors for developing breast cancer (family history of breast cancer, history of biopsies for benign breast disease, age at menarche, and age at first live birth) to predict her chance of developing breast cancer over the next 10, 20 and 30 years.

Mr. Conte. What are the limitations of the model?

Dr. Broder. One major limitation is that there are other risk factors which are not accounted for in the model. Also, like all statistical projections, there is some uncertainty about the predicted probabilities.

Mr. Conte. If this formula holds up, what are the diagnostic and clinical implications for patients and doctors?

Dr. Broder. The implication of this work for patients and doctors is that these calculations should complement clinical experience when counseling individual women about breast cancer screening and prevention strategies, e.g., a woman at high risk might be advised to come for more frequent screening examinations.

These calculations are also useful for designing large clinical trials to evaluate prevention strategies because the size of such trials depends on the absolute risk of developing cancer among the participants.

Mr. Conte. What else is NCI doing to improve early detection of breast cancer?

Dr. Broder. NCI supports the following projects which are geared towards improving early detection of breast cancer.

Development of breast screening plan. NCI has undertaken a planning effort with the Centers for Disease Control and the Food and Drug Administration (FDA) to identify barriers and make recommendations for increasing breast cancer screening and detection.

The focus of this planning effort is to recommend guidelines, identify high risk groups, enhance public and professional education, ensure quality control and follow-up, provide resources, and coordinate and evaluate surveillance activities for future actions.

A series of planning meetings to finalize the recommendations are being discussed in late 1990.

The NCI Mammography Consortium. This consortium consists of six grantees located in communities with 10,000 or more women age 50 and older. The Consortium's objective is to develop innovative programs to increase the use of mammography and clinical examinations.

Public Health Approaches. Entitled: "Public Health Approaches to Breast and Cervix Screening," this initiative seeks to demonstrate how a consortium of community agencies can develop and evaluate strategies to increase the availability, accessibility, awareness, and utility of breast and cervical cancer screening regimens, including mammography, clinical breast examination, breast self-examination, and Pap smears used by low income women, women with low education levels, and minority women over 40 years of age.

Communications. NCI is working to get the message out that use of screening mammography can lower breast cancer mortality. The Office of Cancer Communication has sponsored a Breast Cancer

Awareness Program which is being popularized through the mass media.

Health promotions research. In partnership with the American Cancer Society and linked to professional medical organization, the NCI encourages physicians to screen all eligible women. A new brochure on the working guidelines is being developed to be mailed to all physicians. Through directed program announcements, the NCI will support research which assesses the effectiveness of professional organizations' ability to influence member utilization of these cancer screening guidelines.

Analysis of national data on barriers to breast cancer screening are in progress in order to better design intervention programs. One key message is education: women are generally not aware that breast screening should occur in the absence of symptoms.

Technological improvements for improved quality and increased screening capacity. At present one of the limitations to more wide-spread use of mammography is volume and cost. There is an urgent need to develop a digitized mammogram that is as accurate as our present low dose film screen mammogram. This would allow much more efficient use of a single machine allowing hundreds of mammograms per day as compared to a maximum of 40 per day. It would also greatly enhance the ability of mobile units to take mammography to convenient locations.

Analysis of mammography supply. NCI and FDA staff have jointly analyzed data on supply of new dedicated mammography machines. Findings concerning supply and distribution of machines have been written up and presented. It is clear that the U.S. is well supplied with this technology and communication to the medical community about these issues is forthcoming.

International breast cancer screening data base. In collaboration with investigators from other developed countries, the NCI is creating an international data base on breast screening. It is hoped that the organization and performance of breast screening in countries further along in this process than is the U.S. can help our health care system as screening increases.

Basic research studies. NCI is active in the development of assays to detect breast cancer associated antigens in the sera of patients suspected of having breast cancer. Recently, new oncogenes (neu, int-2) have been discovered that appear to play a role in the progression of breast cancer. Molecular probes to these oncogenes, as well as antibodies to their gene products, are now being used to analyze which "early" lesions may actually be premalignant breast cancer, so that early aggressive treatment can be instituted in those cases.

CANCER VACCINES

Mr. Conte. Dr. Broder, there has been much publicity over the prospects of having vaccines against cancers. I think if we can develop one, that would be a tremendous accomplishment in the war on cancer. But I understand there ~~is~~ are substantial technical difficulties involved. Is a cancer vaccine possible?

Dr. Broder. The prospects for the effective use of vaccines in the treatment and prevention of cancer are good. However, the possibility of producing a cancer vaccine is complicated by the fact that cancer is a diverse set of diseases, some of which are associated with specific etiological agents, such as viruses, and others of still unknown etiology which appear to represent a multi-step disease process. Therefore, it is likely that separate conventional vaccines would have to be designed for each of the various forms of cancer and would have to address their unique etiologies and biological features.

Mr. Conte. What cancers are you looking at which could be prevented by a vaccine?

Dr. Broder. The conventional vaccine approach depends on the ability to identify specific antigens associated with a particular disease entity or neoplasia and to elicit an appropriate protective host immune response to those antigens. Traditional infectious disease vaccines have elicited both humoral (blood) and cellular immune responses to the surface antigens of infectious agents. Thus, for those cancers in which viruses play a major role, a conventional vaccine approach could be feasible. Such a vaccine should be designed to prevent initial virus infection, and additionally could prevent the cancers associated with that virus later in life. An example of a cancer for which this is potentially a successful approach would be the use of the hepatitis B virus (HBV) vaccine to prevent chronic carrying of HBV and subsequent development of hepatocellular carcinoma.

For tumors of non-viral etiology, which presently represent the majority of human tumors, vaccine antigens must be both tumor-specific and applicable to a large segment of the population which is potentially at risk if the vaccine concept is to be workable. Recent work has demonstrated that it is possible to identify a subset of cells in the immune system of cancer patients that specifically recognize the patient's tumor, and that when expanded in tissue culture and then reinfused into the patient, cause regression of the tumor. These TIL (tumor infiltrating lymphocyte) cells represent the current evidence that the human immune system can recognize and kill specific tumor cells. TIL cells constitute the foundation for the NCI's future efforts to employ cellular immunotherapy in a clinical setting. While this approach differs from the conventional strategy of vaccination against a viral disease in that it employs specifically sensitized cells, it is similar in that it incorporates the same principle of destruction of a foreign entity based on specific recognition by the immune systems as is used in producing a conventional vaccine.

In February 1990, the National Cancer Institute awarded its first research project grant for the evaluation of a cancer vaccine. The three-year award is for a Phase III trial of a vaccine which helps prevent post surgical recurrence of an advanced stage of melanoma, the most serious type of skin cancer. The vaccine works by combining melanoma cell membranes and vaccinia (smallpox) vaccine virus to enhance the patient's immune response against melanoma.

OVARIAN CANCER

Mr. Conte. Ovarian cancer is a deadly killer of women. One out of every 70 women in the U.S. will develop the disease and more than 12,000 will die from ovarian cancer every year. Finding an early detector for this cancer will go a long way towards prevention and treatment. What biological markers show promise in the early detection of ovarian cancer?

Dr. Broder. The NCI is making progress in finding methods for early detection of ovarian cancer. A blood test, termed CA125, has been developed and is now in use. This test uses a monoclonal antibody which can detect the ovarian cancer antigen in the sera of patients. To date, it has been used to follow the progress of individual patients to determine if they are free of disease following initial surgery, or if they require further surgery or chemotherapy. Preliminary studies have shown that the CA125 test may also be of some use in detecting early ovarian cancer in asymptomatic patients, i.e., the general population. Recently, this test has been used in combination with two other tests for tumor markers (CA72-4 and CA15-3). These combined tests give greater sensitivity and specificity to the identification of ovarian cancer patients. Larger studies to obtain more evidence for the utility of combinations of these tests are in progress.

The NCI is also working on the use of radiolabeled monoclonal antibodies to detect occult (hidden) ovarian cancer via scanning with a gamma camera. Studies in several institutions have shown that several radiolabeled monoclonal antibodies (including one developed at NCI, B72.3) can now be used to clearly detect ovarian cancer which is not detectable by conventional means, i.e., CT scan or x-ray. Studies on a more basic level are now underway to use specific biologic response modifiers such as recombinant interferon to enhance the expression of target antigens of monoclonal antibodies on the surface of carcinoma cells and to also enhance their shedding into blood. This has recently been shown to lead to more sensitive serum assays, such as the ones described above, and to enhance monoclonal antibody targeting for more efficient detection of occult cancer.

Mr. Conte. I understand that chemotherapy for ovarian cancer may substantially increase the risk of leukemia as much as 12 times - can you comment on this finding?

Dr. Broder. Long-term toxicity, including secondary cancers and leukemia, has been associated with certain cancer therapies. One therapy that was commonly used in the 1960s and 1970s for the treatment of ovarian cancer -- oral melphalan -- has been linked to an increased risk of leukemia occurring three to seven years after treatment. This has raised significant concern about the overall utility and relative danger of this treatment.

As more effective chemotherapeutic agents have become available to treat ovarian cancer, this treatment has evolved and is now quite different from the approach used in the 1960s and 1970s. Rather than giving a simple drug like melphalan by mouth

for prolonged periods of time (up to two years), modern therapy consists of multiple drugs given in a "pulse" fashion (i.e., a monthly basis) for a shorter period of time (usually six months or so). The risk of secondary malignancies resulting from this pulsed therapy is still present but appears to be much lower than encountered with melphalan.

The development of new cancer therapies is concentrated on the identification of more effective, less toxic, regimes. It is now clear that newer therapies for the treatment of ovarian cancer fulfill both of these goals.

NUTRITION AND CANCER

Mr. Conte. NCI has been out front in looking at the links between diet and the development of certain tumors. Can you tell us what have been some of the major highlights of the past year in this research at NCI?

Dr. Broder. The NCI research program in diet, nutrition and cancer prevention seeks to identify ways to reduce the incidence or progression of cancer through dietary modification and chemoprevention. These programs are carried out by intramural and extramural programs of the Division of Cancer Prevention and Control and the Division of Cancer Etiology.

NCI nutrition research is conducted with a variety of approaches:

- through epidemiologic studies of various population groups with distinctive food preparation and consumption patterns;
- by clinical evaluations of dietary interventions;
- in laboratory studies of food content and components; and
- with biochemical/physiologic assessment of nutrient metabolism and absorption patterns in animals and humans.

The NCI is giving substantial emphasis to nutrition in its programs to reduce mortality from cancer. The NCI supports extensive research on the relationship between nutrition and cancer in a wide variety of areas: prevention, epidemiology, etiology, basic cellular mechanisms, therapy, rehabilitation, research development, and information dissemination. Among the many research approaches being pursued, the following are of particular note.

Diet and Cancer. Through epidemiological investigations, assessments are being made about the effects of diet and nutritional status on cancer incidence and survival. Dietary factors under investigation include food groups (e.g., vegetables and fruit), specific foods (e.g., coffee), cooking practices (e.g., frying at high temperatures), and individual dietary constituents (e.g., beta-carotene, vitamin C, folacin, fat, and dietary fiber). Nutritional parameters under investigation include plasma cholesterol, serum fatty acid profiles and serum micronutrient levels. Studies are being conducted in low-risk populations such as Chinese and Japanese migrants to the U.S. who have low rates of breast cancer, and in high-risk populations, such as Blacks who have high rates of prostate, pancreatic, lung, cervical and esophageal cancers. Evidence for the role of dietary and nutritional factors comes from large international variations of cancer incidence, and from studies of migrants, whose cancer rates approach those of the host country during the process of acculturation. Emphasis will continue to be given to investigations to identify and evaluate specific dietary constituents as cancer risk factors. Breast cancer mortality rates among women in China and Japan are about one-fifth those of white American women. Among successive generations of Asian women who have migrated to the United States, however, breast cancer rates have increased to approach those prevailing among Caucasians. The rising trend is suspected to be related to gradual adoption of the Western diet, which is high in meat, fats and calories. This hypothesis is being tested in a population-based case-control study of breast cancer among American women of Asian ancestry, living in Los Angeles, San Francisco and Hawaii. Detailed dietary histories have been collected to assess the role of nutritional risk factors, especially in childhood and adolescence. In blood samples, lipoproteins, fatty acids, micronutrients, and endogenous hormones will be measured to evaluate their relationship to breast cancer risk.

Last year in an area of China whose population is at high risk for stomach cancer, protective effects were noted for vegetables of the allium class, including garlic and onions. This year, a case-control study of stomach cancer in high- and low-risk areas of Italy also revealed protective effects related to the intake of garlic and other fresh vegetables.

Esophageal cancer also occurs more often among Chinese-Americans than Caucasian Americans. Dietary factors continue to be evaluated in Linxian, China, which has the world's highest rates of this cancer. In collaboration with scientists in China, a large-scale, five-year randomized intervention trial continues to evaluate whether certain groups of vitamins and minerals can inhibit late-stage progression to cancer in a high-risk population with multiple micronutrient deficiencies. One component of the trial focuses on persons with esophageal dysplasia and another on villagers from the general high-risk population.

Through chemoprevention and dietary clinical trials, studies are being carried out on the quantitative relationships between food, nutrient intake and cancer incidence. Nutritive and non-nutritive dietary components (i.e., foods and food additives) are being assessed as possible carcinogens and procarcinogens, with attention being directed to interactions in carcinogen metabolism. For example, research during the past year further documented that during the normal process of cooking beef and other meat products, a number of heterocyclic amines are formed that have carcinogenic activity in animals, including non-human primates. These compounds have now been detected in human body fluids following consumption of cooked beef and other meat products. It is clear that these chemicals are consumed by a large proportion of the population of North America and Western Europe and that the methods for the quantitative determination of various heterocyclic amines will need to be further refined. Research on the mechanism of action of this new class of mutagens and their interaction with cellular DNA will be expanded. Studies are planned to evaluate the potential role these chemicals may play in the etiology of human cancer.

Investigators are studying mechanisms by which nutrients affect *in vitro* tumor cell metabolism and growth. Studies are addressing the role of folacin in protein synthesis, the regulation of gene transcription by retinoids, the involvement of vitamin D in inhibiting cell proliferation, the effect of essential fatty acids on colon tumor cell growth and metastasis, and the means by which chemotherapeutic agents alter cholesterol synthesis and cell membrane function.

Methods of food preparation and processing, as well as ingestion of food and vitamin supplements, alcohol, fat and fiber, are being appraised for its role in the promotion of cancer.

Investigators are developing ways of measuring phytochemicals in fruits and vegetables and biological fluids, and assessing chemicals for their potential role in cancer prevention.

An international food component database is being developed to enhance the quality, quantity and worldwide accessibility of nutrient and non-nutrient data for research.

The potential role of obesity and immune dysfunction in cancer risk is being explored through both epidemiologic and laboratory studies.

Researchers are seeking nutritional agents that may serve in the chemoprevention of cancer and are developing methodologies to evaluate the cost-effectiveness of these prevention strategies. The National Collaborative Chemoprevention Projects will continue this year and additional projects will be supported. These collaborative projects are designed to acquire basic knowledge in significant biological systems for anticarcinogenesis. A multidisciplinary approach is being employed in order to derive new insights into practical means for prevention of the process of carcinogenesis and to translate this knowledge rapidly into new chemopreventive entities with known ranges of efficacy and defined pharmacologic and toxicologic properties.

Accurate and reliable means of measuring human dietary intake are being generated. Suitable methods for assessing nutritional status, metabolic patterns, and genetic predisposition are being evaluated for use in epidemiological studies.

Care Management and Nutrition. Clinical aspects of the care and management of cancer patients require focused nutrition research, not on cancer prevention, but on the effective treatment of cancer. Clinical trials are underway to evaluate the effectiveness of nutritional support in the rehabilitation of the cancer patient, nutrition requirements during remission, and nutrient and dietary factors needed to maximize patient survival.

The nutritional requirements of the cancer patient and his or her neoplastic tissues are being appraised, with emphasis on nutrient uptake, utilization and cellular control mechanisms in both normal and neoplastic tissues; and on host-tumor interactions and competition for nutrients. This research helps to develop a more complete understanding of tumor growth and differentiation as it affects the host's metabolism. Knowledge of growth requirements and control mechanisms helps to formulate new therapy schemes based on differential nutrient availability.

In order to develop techniques and procedures to maintain or improve the nutritional status of the patient, various formulations and delivery systems in total parenteral and enteral nutrition and oral supplementation are being examined.

Energy expenditures are also being measured using whole body calorimetry. Behavior modification procedures and pharmacological agents are used to improve the appetite of cancer patients. In addition, laboratory research is underway on the etiology of cachexia, or wasting in cancer patients.

Mr. Conte. What efforts are being made to educate the public on the role of diet and cancer?

Dr. Broder. NCI's Cancer Information Service (CIS) (1-800-4-CANCER) provides free information on diet and cancer prevention. Last year CIS offices answered 203,000 written inquiries, 490,000 telephone inquiries and distributed over 18 million publications to the public. The Office of Cancer Communications develops and disseminates publications on diet, nutrition, and cancer risks; educational materials and programs are being developed on the role of diet and nutrition in cancer etiology, prevention, treatment, and rehabilitation for dissemination to health care professionals and to the public. Through its Cancer Prevention Awareness Program, NCI distributes practical publications that intermediary organizations can use to communicate NCI's dietary guidelines, i.e., booklets, posters, speaker's kit, nutrition training manuals and a complete series of pamphlets developed for the NCI-Giant Food Supermarkets in the point-of-purchase nutrition education program "Eat for Health." The Institute is pilot testing a primary care manual on nutrition to help physicians implement diet modification strategies for their patients during the course of usual office visits. The development of this manual is a joint project of NCI, The American Dietetic Association, American Academy of Family Physicians and the American College of Physicians. NCI places Mass Media Public Service Announcements on Radio and TV, e.g.,"Good News" and "Eat Your Way to Good Health".

Additionally, grants are underway to develop strategies for effective diet and cancer prevention education in the worksite. Currently three groups of investigators are working with over a 100 businesses and industries, including a national telephone and electronics company, to develop and assess nutrition, smoking cessation and employee health behavior programs.

AIDS

Mr. Conte. NCI, along with all the other Institutes, is intensively looking at the underlying mechanism of HIV infection.

What has been some of the spin-off applications of your AIDS research program in looking at cancer?

Dr. Broder. Several efforts in the development of effective drug therapies for AIDS have had provocative applications in the treatment of cancer.

Suramin, an active new agent in the treatment of prostate cancer, was found to have cytotoxic properties during an NCI intramural clinical trial aimed at treating Kaposi's sarcoma in AIDS patients.

AZT, a nucleoside analog and an active drug against HIV, is now being investigated in laboratory studies as an adjunct to some new treatments for colon cancer. This research is studying whether current therapies for colon cancer could be improved with the addition of AZT.

Also, some of the new anti-HIV agents have been shown to inhibit the hepatitis B virus infection in experimental animals. This is a potentially very important observation because the hepatitis B virus plays a critical role in the development of liver cancers in patients with chronic hepatitis.

Epidemiology. As the AIDS epidemic progresses and effective therapies are developed for the treatment of HIV and for opportunistic infections, a new problem emerging is the development of malignancies in AIDS patients, especially lymphomas, skin cancers and others such as liver cancer and anal cancer. The study of these malignancies, their epidemiology and biology, will hopefully give powerful new insights into the process of carcinogenesis. One example of a spin-off that could occur is the development of a vaccine against the Epstein Barr virus. This virus infects many AIDS patients and scientists believe it may play a critical role in the development of lymphomas in the AIDS population.

Biology. The study of the biology and development of Kaposi's sarcoma has lead to the discovery of new growth factors which control the growth of this neoplasm. This work has further invigorated the already robust growth factor research in cancer because it provides an excellent model for future studies. Growth factors play a key role in regulating the growth of several cancers such as breast cancer and prostate cancer, and information about how they operate in Kaposi's sarcoma will aid cancer scientists in their efforts to control these powerful molecules.

Mr. Conte. How are you coordinating your AIDS research with the other Institutes, particularly with NIAID?

Dr. Broder. NCI, NIAID and the other Institutes have several mechanisms in place to coordinate AIDS research at NIH. NCI sponsors workshops on the state-of-the-art in various aspects of AIDS research, such as the development of animal models for AIDS, and invites NIAID and other Institute representatives to these workshops to participate. These workshops are designed to plan for future research efforts and provide a good forum for scientists to exchange insights and coordinate their efforts.

NCI develops Requests for Applications (RFAs) to encourage exciting research opportunities in AIDS. NCI program staff coordinate with NIAID program staff in the development of these RFAs to elicit input and to keep them abreast of NCI efforts.

NIAID scientists participate in the Decision Network Committee which oversees NCI's AIDS Drug Screen. New drugs from the drug screen which are found to be active against HIV are brought before this committee where the data is reviewed and the most promising drugs are chosen for further development.

NCI intramural AIDS clinical trial researchers coordinate with NIAID staff who oversee the extramural AIDS clinical trials program. Important new findings from the intramural program are communicated to NIAID so that they can be considered for development within the AIDS Clinical Trials Groups (ACTGs). NCI and NIAID staff also jointly attend various meetings with industry representatives to discuss future plans for new AIDS drugs.

NIAID, NCI and other Institute staff are invited each year to participate in Dr. Robert Gallo's laboratory meeting where new data on the biology of AIDS including vaccine development are discussed in detail.

NCI, NIAID and all the other Institutes participate in the biweekly NIH AIDS Executive Committee where new developments in AIDS are discussed. The Institutes rotate presentations summarizing their major initiatives and areas of focus.

NCI and NIAID meet monthly with the FDA to discuss issues of drug development pertinent to cancer and AIDS. This forum has proven very useful as a problem-solving arena and has helped expedite the development of some AIDS drugs.

NCI staff participates regularly in NIAID's AIDS Advisory Council meetings and in the ACTG meetings. NIAID staff attend the National Cancer Advisory Board's AIDS Subcommittee meetings held two to three times a year.

INSIGHTS INTO CANCER METASTASIS

Mr. Conte. I hear that NCI has made tremendous progress in looking at how cancer cells migrate from where they started to other parts of the body. You found several proteins that might explain why they migrate to certain organs. How might these findings be useful in the detection, prevention and treatment of certain cancers?

Dr. Broder. Cancer kills the patient primarily because tumor cells escape from the primary tumor, travel in the circulation to distant organs, and initiate secondary tumors called metastasis. Over the past year scientists have made three basic discoveries which provide completely new strategies for potentially inhibiting cancer metastasis formation and growth.

A naturally occurring gene which suppresses metastasis has been discovered. The gene, called NM23, is present in normal cells but is defective in metastatic human cancer cells. The normal form of the gene has been conserved through millions of years of evolution and may normally play a crucial role in tissue organization. In cancer cells the defective NM23 gene produces a defective nm23 protein. This leads to a disorganized state which permits the development of metastasis. Introduction of the normal NM23 gene into cancer cells prevents them from forming metastasis in animals models. A new form of therapy can be envisioned in which the nm23 protein itself is used to treat the patient. In theory the nm23 protein will reverse the tumor cell deficiency, inhibiting cancer metastasis, but having little toxic effect on normal cells which already produce nm23.

A naturally occurring human protein which suppresses tumor cell enzymes required for invasion has been discovered. The complete structure of the new protein, called TIMP-2, and its gene, has been elucidated. One molecule of TIMP-2 can bind very tightly to one molecule of a tumor cell destructive enzyme, called collagenase, abolishing its activity. Abnormal production of collagenase is necessary for tumor cell invasion and growth of new blood vessels to nourish the metastasis. Administration of genetically engineered TIMP-2 is a new form of cancer therapy which is now being tested in animal models. Low toxicity is expected since TIMP-2 is made by normal cells but may be deficient in cancer cells.

A new anti-cancer agent has been developed based on molecular studies of tumor cell migration. A specific biochemical pathway was found to be required for motility and growth of cancer cells. Following a unique screening approach to identify novel compounds which inhibit this pathway, a carboxy-aminoimidazole (CAI) was identified as a potent inhibitor of tumor growth and metastasis. CAI was found to be effective in more than 30 different types of cancer including ovarian cancer, breast cancer, colon cancer, prostate cancer, childhood cancer, leukemia and melanoma.

Mr. Conte. How far down the road before we might see the clinical application of these discoveries?

Dr. Broder. CAI was unanimously approved for clinical development by the NCI Decision Network. Phase I clinical trials using CAI may begin within six months.

PANCREATIC CANCER

Mr. Conte. Pancreatic Cancer is extremely difficult to detect in the early stages, and patients who have it have a very poor prognosis. President Carter's family has suffered tremendously from pancreatic cancer. Can you tell us what NCI is doing in looking at new methods of detection and treatment of pancreatic cancer?

Dr. Broder. The NCI is actively working to develop new methods for the detection and treatment of pancreatic cancer. Several serum assays have been developed and are now being used which can aid in monitoring the progress and in the identification of pancreatic cancer patients. Two types of monoclonal antibody (MoAb) based protocols are being evaluated for effectiveness in pancreatic cancer treatment. The first, developed at the Wistar Institute, involves the use of a MoAb (17-1A) to activate the body's immune system (i.e., idiotypic network) so that the outcome is that the patient actually makes his own antibodies (called anti-idiotype) to the cancer. Some responses in pancreatic cancer patients have now been reported using this MoAb; however, this approach should be considered to be in its infancy. The second approach, which has recently been approved to begin, involves the use of a MoAb-killer isotope conjugate, which has been shown to selectively react with pancreatic cancer.

It should be pointed out that there has been a major advance in the last one to two years in the area of MoAb based therapies. We now have the ability to genetically engineer MoAbs and make them more efficient in tumor killing because we can now humanize them (i.e., remove the mouse protein and genetically insert human protein) and thus give them multiple times without worrying about the patient's immune response to a foreign protein. More importantly, we now have the ability to genetically engineer drugs, toxins or biological response modifiers directly into MoAb molecules, or make them as big or small as needed, to optimize tumor binding, tumor penetration, and tumor killing. These advances should have direct applications in new therapy protocols for pancreatic cancer as well as other malignancies.

The NCI funds a Pancreas Cancer Network which is looking at molecular probes which can better characterize the tumors. In addition, specific oncogenes are being examined which may be able to help distinguish cancer from benign disease.

GEOGRAPHIC VARIATIONS OF CANCER

Mr. Conte. Dr. Broder, what accounts for the wide geographic variations of some types of cancers?

Dr. Broder. A brief review of geographic cancer mortality variations is found in the Atlas of U.S. Cancer mortality Among Whites: 1950-1980, 1987.

It is certain that all of the causes for variations are not known. Possible causes are many, but most would probably fall under a few categories and relate to:

Physician and health providers: Distribution, training, and practice patterns could cause variations in all stages of patient care, through preventive activity, early detection, treatment, and rehabilitation.

Population: Cultural, racial, and age variations between regions affect patient health related behaviors that could contribute to variations in cancer incidence and mortality.

Economic and political variations: Economic, political, and social variations affect the availability of medical are, especially in SES (social and economic status) disadvantaged populations.

Geographic and demographic variations: Variations that affect natural and industrial exposures to carcinogens will also be reflected in different cancer rates.

Mr. Conte. I understand NCI is putting together an atlas of cancer rates in the U.S. How might this atlas be helpful?

Dr. Broder. National cancer maps (or atlases), developed by the NCI, have several important uses. First, they give clues to the causes of cancer. For example, the relationship between asbestos and mesothelioma was found after high rates were found among coastal regions where asbestos had been used extensively in shipbuilding. This is important, for often, if the cause is known, it can be eliminated or reduced. Secondly, these maps identify areas for special cancer control efforts. For example, a high rate of cervical cancer found along the southern border of Texas has recently brought to attention the need for special cancer control efforts in that area. There are scores of other areas with similar needs that can be identified with these maps.

The atlas mentioned above is an excellent resource. A new atlas, The Atlas of U.S. Cancer Mortality Among Non-Whites 1950-1980, is to be published this summer. It's format will be similar to the previous atlas and it will undoubtedly be well received. Both of these have come out of our Epidemiology and Biostatistics Program.

Currently, NCI is working on a project to develop a computerized color atlas of cancer mortality, by country, for every state, from 1968 to 1986. This will give every state a very graphic picture of it's particular cancer problems. These maps can be used in a variety of cancer control efforts. Physician continuing medical education needs (CME) can be tailored to particular cancer control needs, public awareness can be enhanced (particularly in regard to tobacco related cancers), public health officials can better plan programs and target areas for special efforts, and government officials will be better aware of the impact of cancer in their state. Initial reaction to a prototype of this type of map has been enthusiastic. It is our opinion that these maps will stimulate a lot of state and local interest in cancer control.

FLUORIDE STUDY

Mr. Conte. Dr. Broder, will you share with us what is NCI doing to respond to the recent report that asserted that fluoride is a possible cause of cancer in animals?

Dr. Broder. We treat all such reports seriously, and will respond with facts and informed opinion as quickly as possible. A recent National Toxicology Program (NTP) study (not as yet peer-reviewed) of sodium fluoride in F344/N rats and B6C3FI mice of both sexes gave some evidence of osteosarcomas developing in male rats at the intermediate dose of 45 ppm (as fluoride), 1/50; and at the highest dose 79 ppm (as fluoride), 4/80; none at 25 ppm and none in the controls.

The NCI had previously studied and published (Journal of the National Cancer Institute 57: 757, 1976) a study on cancer mortality and incidence statistics for U.S. counties from 1950 to 1969. No trends for any form of cancer, including bone cancer, could be ascribed to the consumption of water that is artificially or naturally fluoridated. It is worth emphasizing that in several areas of the country, drinking water is naturally fluoridated. Several other studies, a total of 21 in the U.S. and abroad, especially in Great Britain, are remarkably consistent in finding no evidence of overall or site-specific excesses of cancer that could be attributed to the level of fluoride in drinking water. This led to the conclusion that "variations geographically and in time in the fluoride content of water supplies provide no evidence of an association between fluoride ingestion and mortality from cancer in humans." We currently have no reason to doubt this conclusion. A few potential disadvantages of the available data should be noted, however. All are descriptive studies based on geographic comparisons. While they are strong studies because of the widespread and often abrupt changes in fluoride exposure, they are nevertheless still based on correlational analyses that are subject to inherent limitations. Secondly, only one other study from England, in addition to the NCI study, included an evaluation of incidence as well as mortality data. While this is not a drawback for the evaluation of most sites, it is a possible concern for bone cancer (suspected on the basis of bioassay data), since this tumor theoretically may be misclassified as a cause of death because of the frequency of bone metastases from a variety of primary malignancies.

The NCI has recently made an examination of time trends in osteosarcomas from the Third National Cancer Survey (1969 to 1971) and the Surveillance, Epidemiology and End Results (SEER) program for the five geographic areas that were common to both surveys. By the end of 1969, the vast majority of the population covered by these five areas was drinking fluoridated water. Statistically speaking, these rates do not appear to be rising over this time period. An analysis of age-specific patterns through 1987 is now underway. Two further analyses are planned. First, the NCI will update its 1976 mortality study with data now available from the 1970s and early 1980s. Second, colleagues from the National Institute of Dental Research and Centers for Disease Control have agreed to provide NCI with the fluoridation status of the geographic regions covered by the SEER areas, at the county level. When these data are in hand, the NCI will determine whether the sort of meaningful epidemiologic comparisons are possible with incidence data as have been carried out with mortality statistics. The NCI hopes to have all analyses completed by June 1990.

NCI'S TOLL-FREE HOTLINE

Mr. Conte. We have heard a lot about NCI's 1-800 number as well as PDQ. Dr. Broder, who has access to these systems?

Dr. Broder. First, let me say that I regard both PDQ, the acronym for Physician's Data Query and the 1-800-4-CANCER service as paramount accomplishments emanating from NCI's efforts in information dissemination.

PDQ is one of the most often accessed databases on the National Library of Medicine's (NLM) MEDLARS computer system which is comprised of 28 scientific and medical databases and distributed to more than 18,000 locations within the United States and in 16 foreign countries. In addition to access through the NLM, the PDQ database is also made available through private vendors; total usage of PDQ, including vendor systems, averages over 1,100 on-line hours and 70,000 searches per month.

The European Organization for Research Treatment in Cancer (EORTC) protocol summaries have been added to the PDQ Protocol File, following extensive discussions between NCI and EORTC staff to ensure that federal standards for the protection of research subjects could be met. PDQ has been mounted on the EORTC's EUROcode network. This system is used by European investigators to communicate data and to randomize patients on EORTC trials.

Mr. Conte. What can they do for a cancer patient? For a physician?

Dr. Broder. PDQ, is a system designed to give immediate cancer related-information to anyone who has access to a computer modem. Physicians can submit a PDQ search through an intermediary who may conduct searches for a number of professionals in a single session.

The system is an on-line database containing up-to-date information on the prognosis, cellular classification, relevant staging, and standard and investigational treatment recommendations for the major tumor types. Summaries of all active clinical trials supported by NCI are in PDQ, along with additional studies submitted by the investigators themselves. Recently, a subfile related to cancer prevention (PDQ-P), has been made available for access through this same system. Another subfile, the PDQ Directory, lists over 15,000 cancer specialists and organizations that provide cancer care.

Regarding the 1-800-4-CANCER toll-free number, anyone with access to a telephone in the United States can call this number and receive up-to-date cancer-related information. This toll-free phone service which is designed to serve the general public, is staffed by trained professionals and is the largest, most visible portion of the Cancer Information Service (CIS). Whenever major events or public issues receive widespread media attention, such as the availability of promising new cancer treatments, the CIS can provide immediate answers to questions from the American public. The CIS consists of a nationwide network of regional offices, 17 of which receive NCI funding, plus a central office which serves those areas not covered by the regional offices. Each day, 1,500 inquiries are answered on the toll-free lines from cancer patients, their families, health professionals, and the general public. Nearly 500,000 inquiries a year flow into the CIS -- nearly three million since it opened in 1976.

The CIS information resources include access to PDQ. Thus, if a CIS professional does not have the information immediately on hand to address a particular concern from a caller, the needed information can be retrieved quickly for the caller by accessing PDQ directly. As use of CIS services has increased, the complexity of the calls and the sophistication of medical information provided has resulted in calls of longer duration, and more use of PDQ.

CONSTRUCTION FUNDING

Mr. Conte. Your budget includes $1.5 million for construction. Is this adequate to meet the needs of the extramural community?

Dr. Broder. The $1.5 million included in the President's Budget is intended to support routine preventive maintenance activities at the Frederick Cancer Research Facility (FCRF). With a facility the size of the FCRF, repairs and preventive maintenance such as heating, air conditioning, and other utilities generally require a minimum of $2.5 million per year. Extramurally, NCI has $11 million in peer-reviewed high-quality construction grant applications available for funding. Authority to assess NIH Institutes, Centers and Divisions for extramural construction was given to NIH last fiscal year by the Congress. To date, NCI has been allocated $2 million of these funds to support two extramural construction grants with the best priority scores.

Mr. Conte. If NCI receives an appropriation in FY 1991 for construction, would the funds be split between the extramural community and the NCI Frederick Cancer Research Facility?

Dr. Broder. If NCI should receive a direct appropriation for construction in FY 1991, dependent upon the level approved, the predominant share would be directed to support the extramural community. Historically, NCI has awarded approximately 80 percent of its construction funds to the extramural community.

NEUROFIBROMATOSIS

Mr. Conte. Dr. Broder, what is NCI doing in looking at the treatment of neurofibromatosis (NF)?

Dr. Broder. Researchers from NCI participate in the NIH Inter-Institute Genetics Clinic, a collaborative effort involving researchers from NCI, NINDS and four other NIH institutes and the NIH Clinical Center. These researchers are currently studying patients with cancer or at high risk of developing cancer to determine the extent of any pre-existing condition or birth defects that may provide clues to the etiology of cancer in these patients or their family members.

The neurofibromatoses comprise at least two distinct disorders: they are designated neurofibromatosis type 1 and neurofibromatosis type 2. The first type is much more common, with one case occurring for every 4,000 live births. The disorder generally appears in childhood with tumors of peripheral nerves and spinal nerve roots, birth marks, freckling in the body creases, and nodules on the iris of the eye. Some types of eye, brain, and muscle tumors are also infrequent manifestations of this disease. The gene for neurofibromatosis 1 has been mapped to the long arm of chromosome 17 by an international consortium of investigators. In cooperation with members of the Mid-Atlantic Chapter of Neurofibromatosis, Inc., an intramural National Institutes of Health team documented an apparent excess of subtle neurological abnormalities which could manifest themselves as learning disabilities in children with neurofibromatosis 1, when compared with their siblings.

Neurofibromatosis 2 is present in one out of every 50,000 live births and is characterized by bilateral acoustic neuromas, which are Schwann cell tumors that arise from the eighth cranial nerve complex. Pressure from these tumors usually causes hearing loss and balance problems in the second or third decade of life. Other central nervous system tumors are common, especially meningiomas and tumors of the spinal canal. The early development of opacities in the lens is a newly described feature of neurofibromatosis 2, which has been mapped to the long arm of chromosome 22. Over the last two years, a total of 25 patients with neurofibromatosis 2 have been evaluated.

Because malignancies are frequent complications of neurofibromatosis, NCI is studying a number of them. Primary among these malignancies are neurofibrosarcomas. Neurofibrosarcomas, malignant tumors of nerve sheath origin, occur in association with neurofibromatosis and account for approximately five percent to 10 percent of all non-rhabdomyosarcomatous soft tissue sarcomas in children. Approximately five percent to 16 percent of patients with neurofibromatosis develop neurofibrosarcoma. The most common primary sites of neurofibrosarcoma appear to be the extremities (42 percent), retroperitoneum (25 percent), and trunk (21 percent).

We will continue to study the molecular genetics and cell biology of neuroblastoma and peripheral neuroepithelioma which are tumors of neural crest origin, as is neurofibromatosis. Our biological understanding of nerve growth factors may be important in neurofibromatosis and treatment of malignancy complications.

Mr. Conte. In the coming year what does NCI plan to do with the Neurology and Deafness Institutes in NF?

Dr. Broder. Two types of studies involving neurofibromatosis 2 are planned through the NIH Inter-Institute Genetics Clinic. In the first study, three subtypes of neurofibromatosis 2 have been hypothesized:

- families with bilateral acoustic neuromas and cataracts;

- families with bilateral acoustic neuromas, multiple meningiomas, and spinal neurofibromas in addition to cataracts; and

- families with bilateral acoustic neuromas, meningiomas, and ependymomas, but no cataracts.

New clinical data will be used to assess the validity of these subtypes as well as to determine whether women with neurofibromatosis 2 have an earlier age of onset of symptoms and an increased frequency of associated brain and spinal cord tumors than is the case for affected men. A second study will use DNA studies to evaluate genetic heterogeneity in neurofibromatosis 2. In addition to genetic linkage studies, tumor DNA from patients will be examined to identify deletions that may precisely map the neurofibromatosis 2 gene.

Neurofibromatosis remains a high priority area for intramural and extramural NIH investigators. The results of these and other studies can be expected to benefit the 100,000 Americans with these disorders, and the biologic insights gained may have implications for many other diseases as well.

Mr. Conte. I am pleased to learn that NCI has produced a report on NF, in response to the Committee's request. Could you summarize the major items of the report?

Dr. Broder. The NCI report entitled "Update on Neurofibromatosis" provides an overview of past and current research efforts into these neurological disorders.

The report notes that since 1980, progress in understanding the origins of the neurofibromatoses has been rapid, catalyzed by research support provided by the NCI, the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute on Deafness and Other Communicative Disorders (NIDCD) as well as by the National Neurofibromatosis Foundation and collaborative research among scientists internationally.

Sustained collaborations between intramural and extramural teams associated with these Institutes as well as the National Eye Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Child Health and Human Development and the NIH Clinical Center have greatly contributed to an improved understanding of the biological and clinical features of the neurofibromatoses. It is now recognized that they comprise two distinct disorders with differing mechanisms of tumorigenesis. Application of these insights to direct patient care is beginning and may lead to prenatal and presymptomatic testing for this disease.

The report also describes ongoing activities at the NIH Genetics Clinic that represent a collaborative effort involving researchers from NCI and five other NIH Institutes. This research is focussed on patients with cancer or at high risk of developing cancer to determine the extent of any pre-existing condition or birth defects that may provide clues to the etiology of cancer in these patients or family members.

ONCOGENE RESEARCH

Mr. Conte. Dr. Broder, oncogene research has revolutionized how scientists look at cancer. The doctors in San Francisco won the Nobel Prize this year for discovering them. What is the future direction of this branch of cancer research?

Dr. Broder. The past 10 years have seen a tremendous increase in our understanding of the genetic basis for the development of cancer. Genetic damage leading to malignancy appears to take one of two basic forms: a change leading to increased activity of growth stimulatory forces within the cell via the amplification or activation of dominant cellular oncogenes or the decreased activity or loss of normal growth inhibitory forces due to deletion or inactivation of suppressor oncogenes. The search for new oncogenes and their functions has uncovered new dynamic elements responsible for the generation of tumors. These are the suppressor genes, which in many instances are the opposite of oncogenes. They are responsible for preventing the uncontrolled growth of cells that is characteristic of cancer. Several such suppressor genes have now been identified. In order for oncogenes to have their effect they must overcome the controlling effects of the suppressor genes.

In the process of tumor formation suppressor genes are either lost or mutated, or attacked by the products of oncogenes and rendered ineffective. In one example, colon cancer, careful molecular dissection of the stages of tumor progression, from its initiation to metastasis, has been achieved. A pattern has emerged where at each stage a new event has occurred; this can be elimination of a suppressor gene or the activation of an oncogene. Each new event takes the cell one step closer to metastasis. Approximately five steps have now been defined. The specific stage of disease can now be determined by examining the specific oncogenes and suppressor genes involved. This should greatly enhance our ability to select appropriate therapies for colon cancer. Research on other specific types of tumors, such as breast cancer, are now rapidly taking advantage of this information to examine the sequence of suppressor gene inactivation and oncogene activation events responsible for these tumors.

The research directions now being taken include identifying new oncogenes and suppressor genes and understanding how the known genes interact to produce tumors. One primary area of future research will be on the genetic changes which set in motion, and perpetuate, the progression of a normal cell to a malignant one. Of increasing interest and importance is the effect that the wide variety of recently characterized growth factors have on fundamental cellular processes such as proliferation and differentiation. The basis of this interest is the potential of therapeutic agents to block growth factor triggering of receptors at the cell surface. Considerable progress has also been made in identifying the targets and intermediary substances in growth factor signaling. Thus, studies on such targets -- protein kinases and G proteins -- will be extended. The knowledge gained during the past year on the mechanisms of action of oncogenes indicates that there may be a large family of regulatory genes with oncogenic potential yet to be characterized. In each case, knowledge of the mechanisms of action of such proteins provides a more rational basis for strategies aimed at cancer prevention and treatment.

A second class of cellular proteins which are important in oncogenesis has been revealed by studies of the familial inheritance of cancer and of the transforming proteins of several small DNA viruses. These proteins are called anti-oncogenes or tumor suppressor genes, because the absence of a functional gene product, rather than its presence, is responsible for transformation. One of the best understood examples of suppressor oncogenes is the Rb gene of retinoblastoma, whose loss or inactivation appears to play an important role in the induction of retinoblastoma. Inactivation of the Rb gene may also play a role in some other commonly occurring cancers of the lung and colon. Loss of inactivation of both copies of the Rb gene in humans may predispose an individual to cancer.

Understanding the molecular consequences of an imbalance between oncogenes and tumor suppressor genes is an exciting challenge in cancer research. This information should also provide new opportunities in early molecular diagnosis of cancer, prediction of prognosis and, finally, novel therapeutic avenues to interrupt the multistage process of carcinogenesis and tumor progression.

The loss of suppressor oncogene activity appears to be responsible for several childhood tumors. Wilms' tumor and retinoblastoma are associated with and indeed may be caused by the inactivation of particular genes. The observation that individuals who survive retinoblastoma or osteosarcoma are at increased risk of developing breast cancer later in life has prompted closer investigation of the role recessive oncogenes play in adult cancers. Over the past year, we have gained important insights into the role of suppressor oncogenes on the development of adult malignancies.

NCI scientists have identified three distinct genetic deletions that are associated with a common adult malignancy -- lung cancer. Loss of a portion of the short arm of chromosome 3 appears to occur in the development of the vast majority of small cell lung cancer cases. This abnormality has been detected in over 95 percent of the small cell lung cancer specimens tested, regardless of whether the sample was taken from a newly diagnosed patient or one who had relapsed. This is clearly the strongest association between small cell lung cancer and any genetic abnormality studied to date. More recently, another chromosomal deletion has been identified in small cell lung cancer: 13q14, the same deletion found in childhood retinoblastoma. But unlike retinoblastoma, in which one inactive gene is inherited, followed by a mutation to the other normal gene, loss of 13q14 gene activity in small cell lung cancers and pulmonary carcinoid tumors appears to be entirely due to somatic mutations that are acquired later in life. Future research in this area will focus on the specific location and identity of the deleted genes. The precise location of the recessive oncogene on the short arm of chromosome 3 is unknown. Future research efforts will be directed at cloning the recessive gene(s) from this region, identifying their protein products, and characterizing their role in controlling cellular proliferation in normal cells.

MULTIDRUG RESISTANCE

Mr. Conte. You mentioned in your opening statement that NCI is taking the lead in looking how certain chemotherapies fail because the body develops a resistance to these drugs. Can you tell us how the body develops resistance to multiple drugs?

Dr. Broder. Intrinsic or acquired resistance to chemotherapeutic agents stands as one of the greatest obstacles to complete tumor eradication and long-term disease-free survival from cancer. One of the most intensively studied examples of this is the phenomenon known as multidrug resistance. This form of drug resistance is characterized by the development of resistance to a wide variety of structurally and functionally diverse drugs after exposure to any one of them. It is now known that multidrug resistance is caused by the increased expression and overactivity of a drug pump, termed P-170 or p-glycoprotein (pgp) in the cancer cell. A number of common drugs, such as verapamil, quinidine, amiodarone, and phenothiazines, are able to block the function of this pump and result in a reversal of multidrug resistance in laboratory experiments. This observation, coupled with the detection of high levels of P-170 expression in tumors obtained from patients with newly diagnosed colorectal, adrenocortical, or kidney cancers or relapsed multiple myeloma, non-Hodgkin's lymphoma and breast cancer, has led to the first clinical trials combining chemotherapy with pgp blocking agents.

The first prospective trial to attempt this was reported this past year at the NCI-supported Arizona Cancer Center. In this trial, eight patients whose multiple myeloma or non-Hodgkin's lymphoma had become resistant to the effects of VAD (vincristine, adriamycin, and dexamethasone) chemotherapy were retreated with the same regimen plus the pgp reversing agent, verapamil. Three of the eight patients responded to this new regimen, all of whom had overexpression of pgp on their tumor cells. This is the first prospective study to demonstrate that the elevated levels of pgp in drug resistant tumor cells are clinically significant and can be overcome by the concurrent administration of pgp-blocking agents. Two trials using a similar strategy to examine reversal of drug resistance in colon, kidney, and adrenal cancers are being conducted by NCI's Medicine Branch. In order to stimulate more prospective studies of this type, the NCI announced a Request for Applications (RFAs) targeting studies of therapeutic correlates of drug resistance. Thirty-four grant applications have been submitted in response to this announcement, and a number will be funded.

Mr. Conte. How might we tailor new therapies to overcome this resistance?

Dr. Broder. An alternative strategy for overcoming drug resistance is to identify drugs that are not susceptible to the inactivation mechanisms used by drug resistant cells. New anthracyclines have been identified that remain highly toxic for cells that are resistant to doxorubicin by virtue of their P170 glycoprotein. These compounds will proceed to clinical trial in 1990 or 1991. A different strategy for controlling drug resistant cells has been shown from recent work at Memorial Sloan-Kettering, where researchers have found that drug-resistant cells are exceedingly sensitive to the action of certain agents such as HMBA (hexamethylenebisacetamide), which promotes cell differentiation. HMBA has produced clinical evidence of tumor maturation in patients with acute leukemia, and will be tested in drug-resistant patients.

New agents are being developed to overcome the various types of drug resistance. For example, buthionine sulfoximine effectively reduces a cellular detoxification molecule and has recently entered into a Phase I/II clinical trial along with another agent, melphalan, for women with refractory ovarian cancer. Clinical trials of aphidicolin which can repair the cellular damage caused by certain cytotoxins and cisplatin are planned for next year.

Future clinical trials will be designed to determine the nature and prevalence of drug resistance in previously treated and newly diagnosed cancer patients. This information may then be used to select a therapy designed to overcome the mechanisms of resistance detected in the patient's tumor. Other clinical trials will assay for drug resistance at the time of initial diagnosis and at the time of relapse or progression so that a clinical correlation may be drawn between the appearance of drug resistance mechanisms in the tumor cells and the development of clinically drug resistant cancer.

Further research to develop more effective, less toxic pgp antagonists is underway. Cyclosporin appears to block the pgp pump in a manner unlike that of other known pgp antagonists. The pharmaceutical industry has screened a number of cyclosporin analogs and identified agents that not only are more potent pgp blockers than cyclosporin but also lack the undesirable immunosuppressive effects of the parent drug. A new derivative of the drug verapamil is scheduled to enter clinical trials in 1990. It appears to have the pgp-blocking capabilities of the parent drug without its adverse cardiac effects. Other monoclonal antibodies, MRK-16 and MRK-17, which are targeted to the p-glycoprotein and significantly inhibit pump function in vitro have been developed by investigators in Japan. This agent is also expected to enter clinical trial in 1990.

NCI/FDA JOINT FELLOWSHIP PROGRAM

Mr. Conte. Dr. Broder, NCI has been a successful pioneer in the field of drug development. I'm encouraged that you are now working with FDA in putting together a training program for doctors and scientists interested in drug development. Can you tell us how the program would work?

Dr. Broder. The successful development of any new therapy for the treatment of cancer requires carefully coordinated efforts on the part of the Food and Drug Administration (FDA), the National Cancer Institute, and the pharmaceutical sponsor. Individuals involved in this process need to possess a broad array of technical and scientific skills including an extensive knowledge of the diagnosis and management of patients with cancer, an ability to interpret preclinical data and apply that data to the design of clinical trials, an understanding of the methods used in the conduct, monitoring, and analysis of results from clinical trials, and a familiarity with the drug review and approval regulations of the FDA. Currently, no formal program exists to provide such a complete and comprehensive training to individuals interested in careers in the field of drug development and regulation. To this end, the Center for Drug Evaluation and Research of the FDA and the NCI have created a joint fellowship training program in regulatory science. This three-year fellowship will consist of one year of primary clinical responsibility on NCI's adult or pediatric oncology service, followed by two years practical training at NCI's Investigational Drug Branch and the Center for Drug Evaluation of the FDA. Fellows will become involved in the development of selected new agents and will be responsible for coordination and analysis of research data leading to new drug approval.

Mr. Conte. Where would the graduates of this program end up?

Dr. Broder. It is anticipated that fellows who complete this training program will be prepared for careers with industry as well as in government. Having individuals with this kind of background involved in the drug regulatory process will likely result in more expeditious development and approval of new cancer therapies. This fellowship also represents the first formal cooperative training effort by the NCI and FDA and will undoubtedly lead to a better understanding and a closer working relationship between the two agencies.

Applications for the fellowship program are now being accepted and the first fellows will enter the program in July 1990.

CLINICAL TRIALS

Mr. Stokes. Dr. Broder, the budget increase proposed for NCI is modest, less than four percent. Throughout your opening statement, you stressed the importance of clinical trials. To what degree will you be able to support needed clinical trials under the President's Budget?

Dr. Broder. The 1991 Budget provides an estimated $238.2 million for clinical trials research, compared to $227.1 million for 1990. This level will allow for continuation of all major clinical trials, as well as for the start-up of 11 major new clinical trials initiatives, including both cancer and AIDS-related trials.

Mr. Stokes. Approximately how many clinical trials are ready to start, but would not be funded under the President's Budget?

Dr. Broder. In 1991, we estimate that there will be about 34 major new clinical trials initiatives that will go unfunded.

Mr. Stokes. Could you give us a few examples of some of the more promising clinical trials that would not be funded?

Dr. Broder. Some very promising research leads have developed through our intramural laboratories conducting clinical research at the NIH Clinical Center. For example, aggressive chemotherapy has shown to be highly effective in eradicating many cancer types, but at the same time it suppresses production of the patient's own immune cells, leading to dangerously low immune cell counts and infections, such as pneumonia, and fever. We have found that by following the chemotherapy with administration of a biologic known as GM-CSF, the bone marrow cell count can be stimulated and the negative effects of the high chemotherapy dosages ameliorated. More research could be supported in this area; it is an area of high-interest since physicians have been limited in chemotherapy dosage because of its deleterious side-effects, including this depletion of the patient's immune system.

Recently, NCI has been able to affect patient accrual rates in a positive sense; we been able to bring more patients into NCI-sponsored research protocols. It is especially important that NCI continue to increase the enrollment of patients from minority or underserved populations in the clinical trials programs. Optimal patient accrual rates translates into quicker data accumulation, and leads to a more timely determination as to study outcome. Last year, about 31,500 cancer patients were enrolled in NCI-supported extramural clinical trials. We still need to increase patient accrual; for example some Phase III trials designed to take two years to complete accrual are taking four to six years. There are clinical trial initiatives that will go unfunded in 1991 which would increase patient accrual to treatment as well as prevention clinical studies.

Other unfunded treatment trials include several studies using photodynamic therapy in ovarian/bladder cancers and mesothelioma, initiatives involving bone marrow transplantations,

and clinical studies on the role of suppressor oncogenes on the course of lung, colon, and breast cancers. Regarding cancer prevention and control research, a number of prevention clinical trials carried out through the community clinical oncology program will go unfunded in 1991. There are also unfunded trials related to AIDS research; one of these unfunded trials would have explored the use of photodynamic therapy to treat Kaposi's Sarcoma, another would have further explored the use of adoptive immunotherapy for the treatment of children afflicted with this disease.

CANCER CENTERS

Mr. Stokes. As you know, the NCI centers program is of great interest to members of Congress. Two centers in Ohio are currently waiting to see whether they will be funded in FY 1990. (These are Case Western's Ireland Cancer Center and Ohio University.) What is the status of the FY 1990 center grant awards?

Dr. Broder. Both grant applications that you mention, Ohio State University and Case Western Reserve, are included within the competing applications pending a funding decision for FY 1990. A funding decision will be made within the next three months.

Mr. Stokes. What is the timetable for making awards?

Dr. Broder. Regarding the funding timetable, the funding plan for FY 1990 is currently under development. After the review of all cancer center core grants that are competing for FY 1990 dollars is completed and the priority scores are known, awards can be made to successful applicants. We should have a plan within three months or so.

Mr. Stokes. The increase for centers would only be $116,000 -- less than one percent -- under the President's Budget. This clearly will not be enough to maintain current services at 56 centers (the level currently funded). If the administration's proposed budget for cancer centers is agreed to, how many centers would lose funding or if the decision is made to keep the number of centers stable, what will be the percentage of downward negotiation required for the current center core grants?

Dr. Broder. Within the funds provided to NCI by the President's Budget, NCI estimates that three or four centers would be phased out; while this option is not desirable it is necessary rather than reducing all awards to the level that it depreciates the value of peer-reviewed recommendations.

If NCI were to maintain the number of centers at 56, we would have to invoke reductions of approximately 20 percent from recommended levels in the competing portfolio of cancer centers. Noncompeting centers would be funded at commitment levels.

Mr. Stokes. Dr. Broder, in your professional judgement, what is the funding level required to adequately support the centers program?

Dr. Broder. The FY 1991 professional judgment budget for NCI supports center requirements at $144 million; $41 million more than the President's Budget. Within this By-Pass Budget, NCI would restore funds for centers phased out in 1989 and 1990, which are expected to resubmit in FY 1991; pay continuing centers at committed levels and competing centers at recommended levels. Under NCI's goal for the Year 2000, plans called for increasing the number of cancer centers by 50 percent. The By-Pass for 1991 adds approximately five new centers throughout the country. Incorporated within the Centers Program are targeted programs supporting prevention, clinical trials, minority demonstration centers, the populace over age 65, and the underserved.

MINORITY HEALTH ISSUES

Mr. Stokes. We know from your testimony last year that you are very interested in reducing the disproportionate share of the cancer burden that minority populations in this country bear.

What specific initiatives is NCI undertaking in this area?

Dr. Broder. Some specific initiatives are as follows:

- Comprehensive Minority Biomedical Support Program including Minority Investigator Supplement, Minority Satellite Supplemental Award, Travel Award for Young Investigators, and High School Summer Student Research Apprenticeships; programs designed to heighten minority interest in cancer research and training.

- Minority Biomedical Research Support Program co-funding with the Division of Research Resources (DRR), provides support for specific cancer-related projects at minority institutions.

- Minority Access to Research Careers (MARC) co-funding with the DRR provides fellowship awards to minority students to pursue training related to cancer and supports honors undergraduate students on MARC grants.

- Cancer Prevention Awareness: The Black College as a Resource develops models to disseminate cancer information to Black populations by working with historically Black colleges. These models would assist in the promotion of educational programs to explore ways to control and reduce cancer risks among Blacks.

- National Black Leadership Initiative is a National Cancer Advisory Board initiative to mobilize the Nation's Black leadership to support NCI goal for the year 2000.

- Prevention Awareness Program for Black Americans is a community-based education project in cities interested in conducting prevention activities.

- Smoking Cessation for Blacks is an intensive community-based campaign for smoking cessation.

- Prevention Awareness Program for Hispanics involves planning and implementation of programs for Hispanics, modeled after Black programs, and development of Spanish language publications.

- Smoking Cessation for Hispanics works with school systems in San Francisco, New York, Boston and Hartford, Connecticut to influence adolescents to stop smoking.

- Use of Mass Media to Reduce Smoking in Hispanics aims to reduce smoking in low income Hispanic populations in South Texas near the Mexican border.

- Intervention Research Among Hispanic Populations improves surveillance to better monitor and determine future cancer control needs for Hispanics.

- Avoidable Mortality from Cancers in Black Populations identify and remedy key factors that contribute to avoidable mortality from specific cancer sites. Behavioral and cultural health system barriers will be addressed.

- Waianae Coast Cancer Control Project will test the effectiveness of community-based and culturally relevant cancer control intervention by utilizing strong Native Hawaiian social and family networks and recognition of "KoKua", a Hawaiian socio-cultural concept, to provide linkages between health workers and Native Hawaiian women.

- Development of Minority Center and Centers Enhancement Award is 1) a planning grant to support development of first minority consortium cancer center and special initiative to award demonstration center in major minority are; 2) a separate award to promote the involvement of minorities in control research to hopefully fully exploit existing research potential at centers with access to large or predominately minority populations.

- Development Research in Special Populations -- Tobacco Intervention Research, and Avoidable Mortality Studies in Native Americans (American Indians, Alaska natives, and Native Hawaiians), Hispanics and Blacks; define cancer control needs of special populations.

- Workshops on Prostate Cancer, Multiple Myeloma and Breast Cancer -- comprehensive workshops will focus on interventions to address the increased mortality in the Black population for these cancers.

- Research Grants to District of Columbia Institutions -- administrative supplements to research grant awards to D.C. institutions for an expansion of studies which address the issue of excess cancer mortality for Black Americans living in the District of Columbia. These are directed at prevention, control, early diagnosis, therapy, and basic research.

- Training, including Cancer Education award to Howard University. Increased efforts to recruit and train minorities in the sciences through the NCI Training Program.

- New Therapeutic Initiative for Minorities, including a Minority-Based CCOP initiative to improve the clinical investigation of cancer therapies for minority patients for both major killers (lung, breast, colon, prostate, and cervix) and diseases of higher relative incidence.

- Epidemiology of Excess Cancers in Blacks population-based, case-control studies on excess rates of certain cancers in Blacks.

- Breast Cancer in Asian-American Women, Black and White Woman, including Molecular Mechanisms study of changes in dietary habits at different stages as basis for differential rates of breast cancer in Asian-American women and risk factors that may account for excess incidence and mortality of Black women due to breast cancer.

- Prospective Study of Human Papillomavirus Infection study of papillomaviruses and excess mortality of Blacks due to cancers of the uterine cervix.

- Recurrence of Mouth and Throat Cancer analysis of factors that affect disproportionate incidence rates of oral cavity and throat cancers in Blacks.

- Case Control Study of Esophageal Cancer in South Carolina study of alcohol use as a contributing factor for excess esophageal cancer in rural Blacks.

- Illiteracy Initiative is a CIS program based at the Medical College of Virginia targeted at Black audiences to increase their participation in all aspects of cancer treatment.

- Reducing Cervical Cancer Mortality in West Virginia has as its long-term goal the reduction of cervical cancer mortality rates in a rural area of southern West Virginia.

Mr. Stokes. Do you feel that progress is being made?

Dr. Broder. It is too early to detect progress as defined by a reduction in the mortality rates from cancer. It is important to note that cancer is not a single entity, there are more than 100 different entities which are "cancers". For most of these cancers, there is a significant lag time between the introduction of an intervention and a detectable reduction in mortality rates. For example, it may take ten or more years before the results of a smoking cessation would be translated into a reduction in lung cancer mortality rates and even longer before a smoking prevention program designed to prevent people from starting to smoke, would result in decreased lung cancer mortality. We are very pleased that an NCI-funded program (The Black Leadership Initiative) has been instrumental in mobilizing community opposition to the targeting of minority men and women for commercial smoking campaigns. Efforts to reduce smoking will certainly play a role in reducing several forms of cancer in Black Americans. However, even though it is too early to detect a reduction in the mortality rates for most cancers, a significant progress towards this goal has been made by the implementation of new research projects and the publication of the preliminary results of programs which were initiated over the past several years. While much more needs to be done, there are a few cancer types where some signs of progress are occurring. For example, age-adjusted ovarian cancer mortality for women under 65 has decreased for both white and Black women since 1973. The same is true for cancer of the cervix, for essentially all age groups.

The new programs which have been initiated during the last several years will eventually effect a significant decrease in the high cancer mortality rates seen among our Black and other minority populations. But some issues are linked to the basic problem of poverty, per se.

Mr. Stokes. What will the Institute spend in FY 1990 in cancer research and control activities that are targeted toward minorities? What is the request for FY 1991 in this area?

Dr. Broder. NCI estimates that $23.2 million will be spent on cancer research and prevention and control activities targeted to minorities in FY 1990. In FY 1991, NCI estimates $25.3 million for these efforts. Related minority activities would increase NCI's funding to $40 million in 1990 and $42 million in 1991.

Mr. Stokes. It has been said that if cancer screening and early detection efforts were used by more Americans, many more lives could be saved. What efforts are being made by your Institute to promote the use of this type of health care in minority communities?

Dr. Broder. NCI is conducting national education campaigns especially tailored to black audiences on early detection such as the Cancer Prevention Awareness Program for Black Americans. NCI has incorporated the National Black Leadership Initiative on Cancer (NBLIC) into its program to provide a structure for community activity around such issues. The theme for the first year of this activity is early detection and screening. NCI is joining with other organizations to promote early detection programs for prostate and breast cancer during the National Minority Cancer Awareness scheduled for April 1990. Our comprehensive cancer centers are now required to develop activity plans for community service and outreach, and these will address the disproportionate incidence and mortality figures in minority populations.

The revitalized Cancer Information Service, reachable by the toll-free 1-800-4-CANCER phone number, is being redirected to be more effective in reaching minority audiences. NCI's Public Health Agency Capacity Building Grants and Data-based Intervention Grants support city health department initiatives to increase the use of cervical and breast cancer screening services in low-income and minority communities. Several investigator-initiated grants have been funded to test methods of improving physician and health clinic outreach in minority communities.

Mr. Stokes. Tell us what you are doing to attract minority students to pursue careers in cancer research. Have you expanded your efforts in this regard?

Dr. Broder. While reviewing and analyzing our current programs directed at minority recruitment, we also obtained information from the recent report of the National Research Council A Common Destiny: Blacks and American Society, the Department of Education's commission report A Nation At Risk and from the 1988 report of the International Association for the Evaluation of Educational Achievement. The deficiencies in the science education and achievement of American elementary and secondary school students is documented in the latter two reports. The gap in schooling quality and achievement outcomes of education for African Americans when compared to White Americans persists according to the National Research Council's report. They also note that the proportion of advanced degrees awarded to African Americans has decreased, that the percentage of African American physicians in the 30 years 1950 to 1983 has only increased from 2.1 percent to 2.7 percent and that African Americans are significantly underrepresented on the science faculties of predominately white colleges and universities.

These facts have led us to focus our training and recruitment efforts towards addressing these issues. We are beginning our recruitment and training efforts earlier in the educational pathway through our Adopt-A-School Program. Through this program, the NCI has entered into a partnership with the District of Columbia's McKinley High School to enrich the school's science curriculum and to motivate the students towards careers in science. The program includes: seminars given by NCI scientists, donation of surplus laboratory equipment, small group after-school laboratory projects supervised by NCI staff, as well as NCI laboratory training during the summer for selected students. This program was successfully initiated this fall and has sustained a high level of involvement on the part of the NCI and the high school faculty at McKinley. As a separate initiative, we will offer year-round preceptorships within NCI laboratories for students selected by the District of Columbia's Board of Education.

The other initiative within our early intervention plan is a pilot project on a Science Camp for Cancer Education. This will provide the opportunity for minority and disadvantaged students to have a summer-long period of intensive training in various scientific disciplines. We hope that this early exposure to science will increase the number of students who choose to pursue advanced degrees in science and/or medicine. NCI scientists were instrumental in developing a science teachers' program. This program, which provides biomedical research experiences for high school science teachers, places a great emphasis on recruiting minority educators who play a key role in promoting an interest in science among their students.

The NCI Office of the Director has been expanded to include a Special Assistant who directly participates in recruiting minority students at all levels. This position is able to participate in recruiting from the standpoint of one who has pursued a career in medicine and in biomedical research. The first aim of this recruitment project is to introduce high school, college and medical students to careers in biomedical research; the second is to introduce them to the wide variety of training opportunities available within the NCI. These goals are being pursued by participation in high school, college and medical school career development programs, attendance at pertinent national meetings, participation in the NIH Visiting Professor Program, and the delivery of scientific talks at college and graduate schools. The Special Assistant also participates in programs to encourage young minority investigators to pursue careers within the NCI, or, extramurally, within the National Cancer Program.

NCI carries out an active recruitment program to offer local high school and college student biomedical training experiences, through the NCI Special Volunteer Program and the Student Research Training Program (SRTP); approximately 40 percent of these students represented minority populations.

In addition, we are actively training and recruiting college-level students to pursue careers in science and biomedical research. The Minority Access to Research Careers (MARC) program provides fellowship awards to minority students to pursue training related to cancer and supports honors graduates on MARC grants through co-funding with NIGMS. During the past year, the NCI provided a supplement to the MARC grant at University of District of Columbia to involve students in summer research in NCI intramural labs. We also support co-funding appropriate MARC Honors Undergraduate Training Grants for summer research training of MARC Scholars in NCI intramural labs. We have approached the University of the District of Columbia, Howard University, Morgan State and other nearby MARC institutions with regard to involvement of their students in NCI research under the co-funding agreement. These efforts would facilitate early identification and selection of MARC students. The announcement of MARC Honors Undergraduate Training Grants for summer research training will be published in the NIH Guide for Grants and Contracts to further the effort to recruit qualified minority students into this program.

The Minority Investigator Supplement provides additional funds to NCI grantees who initiate an application to support minority researchers in their cancer research projects. The awards support minority scientists in their efforts to enlarge their capabilities in cancer research, thereby influencing them to develop independent careers as cancer investigators.

We are also participating in the NIH-supported Minority High School Student Research Apprenticeship Program (MHSSRAP) which seeks to provide high school students with fellowships during the summer for their work in NIH labs.

Concerning National Research Service Awards (NRSA)-Institutional Research Training grants (T32) recruitment efforts, using this mechanism, can be expected to have a significant impact on increasing the number of minority students pursuing a career in research. Institutions are currently required to formulate active plans and procedures for increasing the number of minority candidates for pre- and post-doctoral training supported by NRSA training grants. Applications for these grants must include a description of proposed strategies for increasing recruitment of minority students which is then peer-reviewed and considered by NCI staff as one of the factors in making funding decisions. New applications which do not include a plan are not reviewed. The Principal Investigator is asked to resubmit the application with an appropriate recruitment plan. All competing applications that receive a fundable score, but provide a plan that is judged to be unacceptable, are not funded until they have an approved recruitment plan. Continuing grants that receive a fundable score by peer-review, but do not contain an acceptable plan, are given one year to revise their plan. The plan goes back to the study section for review. If approved, the grant receives funding for the remaining years of award. The Cancer Training Branch staff works with institutions to improve minority recruitment strategies which the reviewers judge to be weak or inadequate.

NCI supports several Cancer Education grants that deal primarily with minority groups. These grants are designed to provide short-term research experiences for college students and high school students. A grant to Howard University supports laboratory research experiences for medical students to encourage them to pursue biomedical research careers. NCI staff will meet with Howard staff to plan an expansion of the program to provide summer laboratory research opportunities for minority students in local high schools.

The Medical Staff Fellowship Program within the National Cancer Institute provides important training opportunities for physicians in medical, pediatric, surgical and radiation oncology. It is also the training ground for many who eventually become intramural investigators within various parts of the Institute. The Clinical Oncology Program is currently formulating plans to increase minority group participation in this program. The goal is not only to train more minority physicians in cancer-related sub-specialties who are prepared for careers in biomedical or clinical research, but also to increase the number of minority physician/scientists within the intramural program of the Institute. The staff of the NCI Laboratory of Pathology make an extensive effort to recruit minority candidates for the Pathology Residency Program. Several of the trainees have chosen to pursue a career in experimental pathology. We are actively recruiting minority physician/scientists to join our senior staff. We are also aware that while recruitment efforts are important, career development and the retention of talented and able minority physicians and biomedical researchers within the National Cancer Program is just as important.

Increasing the number of minority oncologists and biomedical researchers is crucial if we are to transfer state-of-the-art treatment modalities and research advances to those who can most benefit from them. Our efforts directed at minority medical students and house-officers in training are planned to help fill that need. We have established communication with the leadership of the Student National Medical Association, the medical student affiliate of the National Medical Association. We will be a participant in their career development workshop at their national meeting this spring focusing on opportunities in oncology.

We hope to reach out to more and more minority students earlier in their educational and career development process; the evidence supports early intervention as an effective approach. Our further efforts will be developed with this in mind.

Mr. Stokes. I understand that you are undertaking a minority health initiative with the District of Columbia. Can you tell up about this?

Dr. Broder. The District of Columbia has high cancer mortality rates and in response to this, NCI has attempted a special level of "good neighbor" assistance. In collaboration with the D.C. Commission of Public Health, NCI staff are working to promote early detection and state-of-the-art treatments for cancers of the breast, cervix, colon, head and neck. I met personally with Dr. Reed Tuckson on several occasions to discuss these programs. NCI is pinpointing both geographic areas within the District and high-risk groups relative to cancer. Expert assistance has been given to help the D.C. Bureau of Cancer Control analyze census tract and incidence data. NCI staff have provided or arranged for in-service training for nurses, dentists and other primary health providers to improve detection and screening for cancers of the breast, colon, cervix and head and neck. A special "Stop Smoking" contest is being conducted in the District elementary schools. The "adoption" of McKinley High School helps to spread health messages to high school students. NCI is broadly publicizing its training opportunities for minority researchers within the District of Columbia. Accrual of D.C. patients onto NCI clinical trials and participation by minority physicians and biomedical researchers is being encouraged.

NCI is consulting with the D.C. Health Department to create an effective cancer prevention and control plan for the city. Special posters such as a local adaptation of the NCI "Eat Your Way to Good Health" nutrition education poster and two TV announcements using the Washington Bullet's coach, Wes Unseld, have been created and are in use. These videotapes are targeted at young people and designed to discourage smoking.

INTERNATIONAL USE OF PDQ

Mr. Stokes. I understand that NCI will be making information on clinical trials more widely available in Eastern Europe. Can you tell us more about this effort and to what extent this information is generally available in other countries?

Dr. Broder. Besides information available through traditional channels, such as periodicals/journals, conferences, and informal communications, many eastern European countries have or soon will have access to information on NCI-sponsored clinical trials through NCI's database known as PDQ, which is made available through the EORTC (European Organization for Research and Treatment of Cancer) and selected commercial vendors. This information is currently available in western Europe and Israel through the EORTC.

This year NCI will implement a project which will provide access to PDQ and CANCERLIT in compact disc format to at least one cancer institution each in Hungary, Poland, and the Soviet Union. Depending upon the initial results in these three countries and the available resources, NCI also intends to pursue this project in selected other countries in the region. The events in Eastern Europe are quite fluid and our plans, therefore, must be flexible.

At the present time, PDQ is not generally available in Latin America, Africa, or Asia. It is anticipated that this situation will change in the near future, with the increased availability of PDQ in compact disc format.

GENE THERAPY

Mr. Stokes. In your opening statement, you spoke of a new technique that involves inserting new genetic material into human cells, returning the cells back to the patient and tracking them. How does this work and what does it accomplish, in layman's terms?

Dr. Broder. For the past 10 years, NCI's Surgery Branch has been attempting to develop new approaches to cancer treatment in which the body's own immune system is used to fight cancer. These studies involve the removal of immune cells, called lymphocytes, from a patient's body, growing them in large numbers outside of the body in cell culture, "educating" these cells to react against the cancer and then returning them to the patient where they seek out and destroy cancer cells. This approach, called adoptive immunotherapy, achieved its first success in causing cancer regression in humans in 1985. More recently, the Surgery Branch has developed cell transfer therapies for the treatment of patients with advanced cancer that involve the growth of immune cells that are extracted directly from tumors. These tumor infiltrating lymphocyte or TIL cells have potent antitumor activity and when transferred back into the patient, can cause cancer regression in approximately one-half of patients with malignant melanoma.

In an attempt to "activate" TIL cells so that they become even more effective in killing tumor cells, NCI scientists in conjunction with the National Heart, Lung, and Blood Institute have begun the first clinical trial in which a foreign gene is inserted or "transfected" into human cells that are then administered to a patient. This study involves insertion of the gene that confers resistance to the antibiotic neomycin into TIL cells that are grown in culture prior to their infusion. This initial study is examining the feasibility, along with the technical aspects, of the transfer of genetic material into human cells. Preliminary analysis of the first few patients treated has found transfected TIL cells in tumor deposits as early as four days following infusion. These cells remain detectable in tumor tissue for several weeks and in the peripheral blood for up to two months and there does not appear to be any altered or unexpected toxicity attributable to them. Future studies will examine the insertion of additional genes such as those that code for tumor necrosis factor (TNF) or Interleukin-2 (IL-2) into TIL cells in an attempt to further enhance their antitumor activity.

The implications of this study are far-reaching. If new genes can successfully be inserted into human cells, this may provide a new avenue for the treatment of a variety of diseases caused by the inactivity or absence of certain genes, such as sickle cell anemia, cystic fibrosis, and alpha-1 antitrypsinase deficiency, among others. The development of "gene therapy" is one of the most promising and exciting frontiers in all of medicine as we enter the 1990s.

Mr. Stokes. What are the practical applications of this research? I understand that it may be useful in treating Sickle Cell Anemia.

Dr. Broder. There are many potential practical applications of research in gene transfer and gene therapy. The work discussed above is involved with developing better cancer treatments by taking immune cells from patients and genetically modifying them so that they have more active anti-cancer activity before returning them to the patient. The gene modification of lymphocytes can also be used to introduce genes that may correct other diseases. If new genes can successfully be inserted into human cells, this may provide a new avenue for the treatment of a variety of diseases caused by the inactivity or absence of certain genes, such as sickle cell anemia, cystic fibrosis, and alpha-1 antitrypsinase deficiency, among others. The development of "gene therapy" is one of the most promising and exciting frontiers in all of medicine as we enter the 1990s.

CERVICAL CANCER

Mr. Stokes. How is NCI working to improve screening for cervical cancer and to increase its use?

Dr. Broder. In 1989, NCI spent approximately six million dollars on cervical cancer screening and $17.7 million overall on cervical cancer research. Subject areas included epidemiology, etiology, diagnosis, treatment, and control.

A number of awards address cervical cancer screening in inner-city and rural populations. Outreach methods that target hard-to-reach populations are being developed and tested through these grants. Additionally, proposals currently are under review in response to an RFA entitled, "Public Health Approaches to Breast and Cervix Cancer Screening."

Cervical cancer screening is a complex problem because those women who are not being screened frequently are the ones who are not in the medical system, or who are not receiving preventive care. Those women are most likely to be older, poor, and are frequently from minority groups. It is vitally important that the needs of these disadvantaged women be met, particularly with respect to cervical cancer screening. The success of cervical cancer screening efforts also depends on a sensitive recognition of diversity and cultural traditions of various populations. NCI will continue its efforts to increase the access of these hard to reach populations to cervical cancer screening by developing innovative new ways to bring this important message to local communities and promote the use of pap smears for these disadvantaged women.

Mr. Stokes. Do you work with the Centers for Disease Control in this effort?

Dr. Broder. To address this complex problem, the NCI and the Centers for Disease Control are conducting a review of the status of cervical cancer control. Included are identification of weak points in the system at the level of recruiting of women for screening; obtaining, processing, and reporting of cervical smears; and effective follow-up and treatment.

A background paper has been prepared, and is undergoing review by intramural and extramural experts. A revised document incorporating recommendations for actions at the Federal, state, and local levels -- both governmental and private -- is scheduled for July 1, 1990.

CLINICAL TRIALS

Mr. Stokes. To what extent are minorities represented in clinical trials conducted by NCI? I understand that you are trying to increase representation of minorities in clinical trials.

Dr. Broder. There is currently a new effort to document the representation of minorities in therapeutic clinical trials in the Clinical Cooperative Groups and to increase their participation in these studies. Our initial estimates indicate that approximately 12 percent of the nearly 31,000 individuals entering clinical trials in 1988-1989 were minority patients. Now all Cooperative Groups will record the racial or ethnic type of each minority patient participating, so that quantitative comparisons will be possible.

Data from the Community Clinical Oncology Program (CCOP) indicate that minorities represent seven percent of patients enrolled in clinical research. The data also indicate that when access to treatment-clinical trials is provided, minority patient enrollment on protocols is similar to that of white patients. These findings suggest that a major factor influencing participation in clinical research by minority patients is access to the clinical trials process.

The CCOP model is an effective mechanism for facilitating the linkage of investigators and their institutions with the clinical trials network, and is being used to extend the benefits of cancer clinical treatment research to minority populations. A request for Applications (RFA) for a Minority-Based Community Clinical Oncology Program was issued in May 1989. Applicants to this RFA were required to have access to a large minority cancer population, i.e., greater than 50 percent of new cancer patients from minority groups. Awards under this program will be made by June 1, 1990.

The Clinical Cooperative Group program is also pursuing new means of increasing minority representation in these studies.

Supplemental funding will be given to selected major minority centers (such as Meharry Medical School and University of Puerto Rico) in order to provide the staffing and expertise to perform clinical studies. Close cooperation and assistance will be offered by established cancer centers and institutions experienced and skilled in this type of research.

Particular attention will be given to those diseases most affecting minorities -- lung, breast, prostate, and colon cancer; as well as those disease of higher incidence in such populations -- esophagus, cervix, myeloma, stomach cancers, etc. Important benefits can be offered to minority patients while knowledge is gained about promising therapies.

PEDIATRIC AIDS

Mr. Stokes. How many clinical trials are currently being supported in the area of pediatric AIDS?

Dr. Broder. Four pediatric clinical trials are closed with continuing followup; six are currently open and recruiting patients. Three trials are planned to open in 1990 to 1991.

Mr. Stokes. Are you pursuing any new leads in this area?

Dr. Broder. HIV infection in children is the most rapidly growing area of AIDS disease. NCI's Pediatric Branch is a world leader in the development of new therapies to treat children infected with the AIDS virus. Studies done at NCI were pivotal in leading to the Food and Drug Administration's (FDA) recent approval of AZT as an effective treatment for pediatric AIDS.

In addition to helping to stabilize the progressive immune dysfunction of HIV infection, AZT also improves the HIV-related neurologic dysfunction enabling children to better achieve their developmental milestones. A new and exciting lead in the treatment of pediatric AIDS is the development of a second drug, dideoxyinosine (ddI) which also appears effective against HIV infection in children. An NCI priority is the development of new regimens utilizing both AZT and ddI to improve treatment efficacy and to study whether resistant strains of HIV develop with such combinations. Other new leads in treatment include soluble CD4 and dideoxycytosine (ddC) alone and in combination with biologic molecules such as gamma interferon and the colony stimulating factors. Researchers now have a variety of promising compounds available to design increasingly effective treatment strategies for pediatric AIDS.

One critically important new approach being pursued at NCI is the effort to interrupt the maternal-fetal transmission of HIV during the intrapartum period (labor and delivery) when much of the transplacental transmission is believed to occur. The Pediatric Branch is studying the toxicity and efficacy of CD4, a molecule which binds to HIV, preventing the virus from infecting human cells in HIV-infected infants and children. Once safety and efficacy have been established in these patients, pregnant HIV-positive mothers will receive infusional CD4 during the intrapartum period and the newborn will receive CD4 for 24 hours after birth. This trial will serve as a pilot study for a subsequent larger scale study to investigate the efficacy of CD4 as prophylaxis against maternal-fetal transmission.

Another new lead regarding maternal-fetal transmission has emerged from a large study of the natural history of HIV infection in pregnant women and their offspring being carried out in collaboration with the National Institute of Child Health and Human Development (NICHD) and the State University of New York Health Sciences Center. Preliminary analyses indicate that HIV-infected women transmit the virus to approximately 30 percent of their offspring, with premature babies appearing to be at three-fold higher risk than full-term babies. Also of note is the preliminary finding that mothers who transmitted HIV to full-term babies had very low or absent antibodies to one of the HIV proteins, gp120. Mothers of uninfected full-term infants appear to confer immunologic protection against HIV infection to their offspring via a high-affinity antibody to gp120. Expansion and follow-up of this finding is important because this information has relevance for vaccine development and for potential perinatal immunotherapy.

Mr. Stokes. To what extent are pediatric patients included in your AIDS clinical trials?

Dr. Broder. A major effort has been made to recruit and treat pediatric AIDS patients on clinical trials at the NIH. This effort has resulted in the accrual of the 220 patients to trials -- the largest number of pediatric patients on AIDS trials in the United States. These patients accounted for 29 percent of our inpatient service in 1989 and 23 percent of our outpatient service. The NCI Pediatrics Branch has emerged as one of the most important research units in pediatric AIDs in the world.

Mr. Stokes. What do your studies tell us about children born to HIV-infected women?

Dr. Broder. HIV infection in children is the most rapidly growing area of AIDS disease. A new lead regarding maternal-fetal transmission has emerged from a large study of the natural history of HIV infection in pregnant women and their offspring being carried out in collaboration with the National Institute of Child Health and Human Development (NICHD) and the State University of New York Health Sciences Center. Preliminary analyses indicate that HIV-infected women transmit the virus to approximately 30 percent of their offspring, with premature babies appearing to be at threefold higher risk than full-term babies. Also of note is the preliminary finding that mothers who transmitted HIV to full-term babies had very low or absent antibodies to one of the HIV proteins, gp120. Mothers of uninfected full-term infants appear to confer immunologic protection against HIV infection to their offspring via a high-affinity antibody to gp120. Expansion and follow-up of this finding is important because this information has relevance for vaccine development and for potential perinatal immunotherapy. Since only a third of infants born to infected mothers appear to actually become infected, it is important to find out what maternal, viral or infant factors are involved in the risk for infection. Are there specific strains of the virus that are more likely to be transmitted to the fetus? Does the timing of the infection have an impact on the clinical manifestations which evolve and does this affect the child's prognosis? These and many such questions have a major impact on approaching the development of strategies that might block or prevent the infection of the fetus or infant. For example, if transmission could be blocked by early treatment with a drug like AZT or soluble CD4, does it need to be given early in pregnancy, late in pregnancy or at the time of labor and delivery?

One critically important new approach being pursued at NCI is the effort to interrupt the maternal-fetal transmission of HIV during the intrapartum period (labor and delivery) when much of the transplacental transmission is believed to occur. The Pediatric Branch is studying the toxicity and efficacy of CD4, a molecule which binds to HIV, preventing the virus from infecting human cells in HIV-infected infants and children. Once safety and efficacy have been established in these patients, pregnant HIV-positive mothers will receive infusional CD4 during the intrapartum period and the newborn will receive CD4 for 24 hours after birth. This trial will serve as a pilot study for a subsequent larger scale study to investigate the efficacy of CD4 as prophylaxis against maternal-fetal transmission. Although some of these questions can be addressed in clinical studies, basic laboratory models, including experimental animal models, will be of considerable importance.

In addition to understanding the timing of vertical transmission, it is important to develop techniques for prenatal diagnosis as well as for diagnosis at the time of birth. The latter is of critical importance to deciding which infants require early therapeutic intervention.

In infants who are infected, studies that delineate the basic abnormalities of the immune system are of importance as are studies to discern where the virus is residing in the body. Research aimed at improving the diagnosis, treatment and prevention of the bacterial, viral, parasitic and fungal infections which occur in infants and children is of considerable importance. These studies will require the use of novel combination regimens, paralleling the insights gained from the successful treatment of childhood cancer.

Mr. Stokes. Can you make any generalizations?

Dr. Broder. At this time it is unclear as to when HIV crosses the placenta to infect the fetus. As noted above, preliminary analyses indicate that HIV-infected women transmit the virus to approximately 30 percent of their offspring, with premature babies appearing to be at threefold higher risk than full-term babies. Data exists demonstrating that infection of the fetus can occur during the first trimester. However, it is also quite likely that a considerable amount of the transmission occurs during the intrapartum period, i.e., labor and delivery. If intrapartum transmission does occur, this would lend itself to the possibility of blocking transmission. Agents like soluble CD4 might provide a mechanism to block transmission. The Pediatric Branch will initiate clinical studies with rCD4 during the intrapartum period to determine the safety and kinetics of rCD4 during labor and delivery. This data will provide a basis for future clinical and preclinical studies.

CHILDREN'S INN

Mr. Stokes. What is the status of the Children's Inn?

Dr. Broder. During the past year, great progress has been made toward achieving a long-term goal, the establishment of a home for families of children who are undergoing treatment at the NIH. The Children's Inn is a 32,000 square foot dwelling in a lovely tree-lined setting on the NIH campus. It is ideally located to provide a peaceful and comfortable place for families to stay at while their children are receiving treatment at the NIH. It has been designed so that families can attain privacy as well as support and comfort from other parents and friends. In addition to its many services, The Children's Inn will contain 36 family rooms. Each room will house two double beds (or when necessary, a crib) and will have a full bath. There are common kitchens, playrooms, sitting rooms, game and computer rooms, a library, and meeting rooms. Designed by a multidisciplinary team of specialists, The Children's Inn will serve as a model to the nation for the work of a support facility for children and families undergoing a difficult medical crisis that forces them to be displaced from the support of their homes, family and community. The Children's Inn also represents the productive and creative interchange and interaction of the Government with industry and the private sector. Construction began in late December 1988, and completion of the Children's Inn will be in June 1990.

Mr. Stokes. How much money has been raised from non-government sources for this project?

Dr. Broder. Overall, more than $4.6 million has been raised, through the NIH, from private fund raising efforts for The Children's Inn. This has been an excellent example of public/private cooperation.

ANTI-SMOKING CAMPAIGN

Mr. Stokes. Has NCI been involved in the secretary's anti-smoking campaign? I would imagine his visibility on this issue will give your effort a shot in the arm.

Dr. Broder. NCI's Division of Cancer Prevention and Control and Office of Cancer Communications have been involved in a number of activities during the 1980s that have served as the foundation for the current anti-smoking campaign of Secretary Sullivan. During Dr. Sullivan's tenure on the NCI's National Cancer Advisory Board, prior to becoming Secretary of DHHS, he provided leadership in a number of NCI smoking and cancer prevention-related activities which focused on minorities. Most noteworthy, in March 1988, he chaired the NCI co-sponsored Conference on Tobacco Use Among Blacks and Hispanics. The specific issues faced by various minorities in smoking prevention and control have been under study since 1985 through a number of NCI-funded research grants and contracts. Investigators from these projects have formed the core for an informed minority leadership and have provided important scientific information that resulted in public actions against the Uptown cigarette brand and concern over the targeting of various minorities by the tobacco industry. The NCI will continue to work with the Secretary, DHHS and the Office on Smoking and Health to reduce the elevated cancer burden among ethnic minorities through the prevention and control of cigarette smoking.

With respect to Dr. Sullivan's recent actions related to women and smoking, the NCI has been a primary co-sponsor of the Women versus Smoking Network and a leader in research on specific issues related to smoking prevention and control among women. In the past, NCI worked closely with the Advocacy Institute, which is leading the current public education activities related to the new Dakota cigarette brand. The NCI has been monitoring with great concern the epidemic rise of lung cancer among women (which has now replaced breast cancer as the leading cause of cancer death among women). Current research and education activities of the NCI are focused on reducing this lung cancer epidemic.

In all of the areas being addressed by Secretary Sullivan, NCI's Office of Cancer Communications (OCC) has worked closely with the Office on Smoking and Health to support the Secretary's campaign, distributing information materials to help smokers quit through the Cancer Information Service and other intermediary groups. A booklet describing community action techniques to bring attention to the anti-smoking effort was also developed and disseminated by OCC. Additionally, OCC disseminates materials that are produced by the Division of Cancer Prevention and Control's research program including manuals to help physicians and health professionals assist their patients in quitting, and guidelines for the use of media, school-based smoking prevention curricula, and pamphlets to help smokers quit. Dr. Sullivan's commitment has been a significant moral booster to NCI staff.

CANCER CENTERS

Mr. Early. Doctor, if the proposed request for centers is agreed to, would any centers lose funding?

Dr. Broder. NCI is currently exploring ways to ensure that scientific excellence continues within the centers program while negotiating reasonable reductions from the peer-reviewed recommended funding levels for competing centers, or our commitment levels for noncompeting centers. Our goal is to maintain the stability and availability of resources for all centers, including newly proposed centers. If NCI is faced with the challenge of seriously depreciating the value of peer-reviewed recommendations by invoking large downward negotiations, we would reluctantly be forced to reduce the numbers of centers which are supported. Most experts fear that choosing significant downward negotiations in order to preserve the number of centers is self-defeating in the long run.

Mr. Early. If the number of centers is maintained, what will be the percentage of downward negotiations required for current center grants?

Dr. Broder. Based on the level contained in the 1991 President's Budget, and to maintain the current number of 56 cancer centers, NCI would have to reduce competing centers by approximately 20 percent; noncompeting centers would be paid at commitment levels.

CLINICAL TRIALS

Mr. Early. Doctor, will you have to curtail any ongoing clinical trials with your FY 1991 budget? If so, which ones?

Dr. Broder. While none of the National Cancer Institute cancer or AIDS trials will be terminated in FY 1991 due to budgetary restrictions, some clinical trials will proceed at a slower rate because of the need to balance competing initiatives. Even though these clinical trials will be completed, the data-accumulation phase of the trial will take more time, delaying the final outcome of the study.

Mr. Early. Are there any high priority clinical trials which are ready but cannot be initiated because of lack of funds in the FY 1991 request? If so, please provide a list of these, along with a brief description and the associated costs, including first year cost.

Dr. Broder. Yes, while NCI will be able to initiate 11 major new clinical trials, there are a number of initiatives which will remain unfunded in the FY 1991 request. THe following listing outlines these unfunded clinical trials:

MAJOR NEW CLINICAL TRIAL INITIATIVES - CANCER
FY 1991: Unfunded Within President's Request
(dollars in thousands)

TREATMENT/DETECTION/DIAGNOSIS:	First Year Cost	Total Cost
Trans-retinoic Acid and other Biologicals in Children with Leukemia and Selected Solid Tumors	500	1,500
Early Empirical Antifungal Therapy in Febrile Neutropenic Patients	300	900
GM-CSF for the Management of Patients with Fever and Neutropenia	2,000	6,000
Purigenic Receptor Agonist in Prostate Cancer	200	600
Attainment of Optimal Patient Accrual Rates in Contract-Supported Clinical Trials	2,700	10,700
Clinical Trials of Novel Therapeutic Agents (oligo-deoxynucleotides and immuno-toxin conjugates)	3,500	9,000
Trial of Anti-growth Factor Therapy in Multiple Myeloma, Malignant Melanoma, Ovary and Prostate, Including Use of Suramin and Suramin Analogs	3,125	8,250
Increased Accrual of Minority and Other Underserved Populations in Clinical Trials	4,000	12,000
Increased Accrual onto High Priority National Clinical Trials, Including Patients Over Age 65	7,000	21,000
Expansion of Adoptive Immunotherapy/combination Cytokine Trials/Gene Transfer Studies	2,500	6,500
Evaluation of the Role of Suppressor Oncogenes on Lung, Colon and Breast Cancers	1,000	2,000
Trial of Photodynamic Therapy in Refractory Malignancies (including ovarian/bladder cancers and mesothelioma)	850	2,475
Expansion and Follow-up of Adjuvant Therapy Trials in Breast, Colon, and Rectal Cancers	2,000	6,000
Expanded Correlation in Clinical Trials with Laboratory/Basic Science Studies	2,000	6,000
Bone Marrow Transplantation Initiatives	1,000	3,000
Development of Diagnostic Imaging to Study Perfusion	600	1,800
Digitalization of Chest Radiography	450	1,350
Radiolabelled MoAb Studies	1,000	3,000
Synthesis of Compounds for Boron Neutron Capture Therapy	475	1,425
Imaging of Bone Marrow Tumors	500	1,500
Clinical PET Studies of Brain Tumor Metabolism	900	2,700
Use of Fludarabine for Treatment of Low Grade Lymphomas	400	800
Clinical Application of Monoclonal Antibodies in Diagnostic Studies (Expansion)	1,000	2,000

PREVENTION & CONTROL		
Funding of eight additional Minority-based CCOPS, Increasing Minority Patient Accrual..........	1,200	3,600
Prevention Clinical Trial within CCOPS/Groups Network........................	4,000	12,000
Finland Study - additional resources for serum bank..............................	934	934
Fund Additional CCOPS to optimize patient accrual............................	8,400	25,200
Women's Nutrition Health Trial.................	15,000	150,000
CORE SUPPORT FOR CLINICAL RESEARCH:		
Increased Support for Clinical/Comprehensive Cancer Centers.............................	33,000	165,000
SUBTOTAL, FY 1991 Unfunded Cancer Trials.......	100,534	467,234

MAJOR NEW CLINICAL TRIAL INITIATIVES - AIDS
FY 1991: Unfunded Within President's Request
(dollars in thousands)

	First Year Cost	Total Cost
Adoptive Immunotherapy in Children with AIDS (Expansion)........................	1,000	5,000
B1 Antibody for Treatment of B-Cell Lymphoma Associated With AIDS (Expansion).............	500	3,000
Clinical trials of novel therapeutic Agents (immunoconjugates, oligonucleotides, nucleoside analogs).........................	11,200	22,400
Trial of Anti-growth Factor Therapy...........	375	750
Trial of Photodynamic Therapy in Kaposi's Sarcoma..	500	1,275
Development of Diagnostic Imaging Strategies in AIDS	800	2,400
Digitalization of Chest Radiography...........	150	450
Treatment of High Grade Lymphomas and AIDS.....	200	400
SUBTOTAL, FY 1991 Unfunded AIDS Trials.........	115,259	502,909
TOTAL, FY 1991 Unfunded NCI Trials............	$114,509	$500,659

CANCER PREVENTION SCHOLARS PROGRAM

Mr. Early. Bring us up to date on the Institute's Cancer Prevention Scholars Program. How much has been budgeted for this program in FY 1990 and FY 1991, and how many scholars do you expect to support?

Dr. Broder. The Cancer Prevention Fellowship Program is currently undergoing a major recruitment effort in response to the need for physicians and other scientists to be trained in cancer prevention and control. Currently there are ten fellows. As of July, 1990, eight new fellows will begin, bringing the total to 18. We expect an additional eight more fellows in July 1991. The program budget for FY 1990 is $830,000 and for FY 1991 is $1,023,000.

PROFESSIONAL JUDGMENT BUDGET

Mr. Early. Doctor, in your professional judgment, given the opportunities before us, is your budget request in line with these opportunities?

Dr. Broder. My opinion is that the budget for the National Cancer Institute that you have before you will permit the Institute to continue the initiatives and programs in a manner that will permit continued progress in the cancer field. However, I would be remiss if I did not tell you that the current activity in cancer research has never been more explosive and promising. It is my professional judgment that many opportunities exist that could be explored further to the benefit of the American people.

STATE AND LOCAL HEALTH DEPARTMENTS

Mr. Early. What progress has been made since improving prevention and outreach programs with state and local health departments?

Dr. Broder. In 1984, the NCI began an active effort to involve all agencies in developing initiatives and programs that are needed to achieve major reductions in cancer incidence, morbidity, and mortality. As part of this effort, the Cancer Control Applications Branch has undertaken development of a variety of grant assistance programs for health departments to improve their technical capacity for implementing cancer prevention and control programs, and to demonstrate various approaches that may be used by other states. Several major programs are underway and have stimulated cancer prevention and control initiatives in 22 states in nutrition, smoking prevention and control, screening and detection, and state-of-the-art treatment.

The program entitled "Technical Development in Health Agencies" encourages knowledge and skill development among health department staff while implementing prevention and outreach programs. Another program entitled "Data-based Interventions for Cancer Control" aims to stimulate the use of available data related to cancer control for planning and implementing programs based on local priorities, resource needs, and priority areas of cancer control. More recently, another grant program for health departments has been initiated to develop strategies to increase the proportion of low income, low education level and minority women over the age of 40 who receive screening for breast and cervical cancer. NCI believes that these program will facilitate local health departments in their efforts to successfully implement cancer prevention and control initiatives, thereby reducing cancer incidence and mortality rates. NCI will continue to work with health officials from the various states and the District of Columbia on these initiatives.

Mr. Early. How many states and local health departments are now participating in these efforts?

Dr. Broder. Twenty-two state and local health agencies are currently participating in these efforts and additional agencies will be added to the program in FY 1990. Since 1986, nine grants have been funded that are related to technical development in health departments (eight states and one county) the purpose of which is to build the public health department's capacity to provide cancer prevention and control services. Six state health departments have been funded since 1987 under the Data Based Interventions Program. Seven other state health departments and the District of Columbia have been funded since 1989, and additional health departments will be funded in 1990 under this program. The FY 1990 grants to health departments that focus on breast and cervical cancer screening are currently undergoing peer-review.

PEDIATRIC AIDS

Mr. Early. How much is NCI allocating for pediatric AIDS research in FY 90 and 91?

Dr. Broder. The National Cancer Institute is projecting an estimated $7.9 million for pediatric AIDS research in FY 1990 and $10.2 million in FY 1991. There are a great many exciting opportunities available for exploitation in this important area of research. NCI may direct a greater share of funds to this area before the end of FY 1990.

Mr. Early. Briefly highlight what your program plans are for FY 1991?

Dr. Broder. The Division of Cancer Treatment plans to significantly expand its Pediatric AIDS program in FY 1991. The Pediatric Branch of NCI hopes to study the pathophysiology of HIV related dementia and to assess the relative benefits of continuous infusion AZT versus intermittent AZT versus ddI on reversing neurodevelopmental deficits. These studies will attempt to optimize our treatment of children while also shedding light on the disease abnormalities which occur.

A study on the perinatal transmission of HIV, carried out in collaboration with the National Institute of Child Health and Human Development and the State University of New York Health Sciences Center, will be expanded. A study on the natural history of HIV-associated AIDS in pregnant women and their offspring will continue. Preliminary analyses indicate that HIV-infected women transmit the virus to approximately 30 percent of their offspring, with premature babies appearing to be at three-fold higher risk than full-term babies. This study will be expanded in FY 1991 to include an intervention component to determine whether perinatal transmission of HIV-1 can be prevented. Potential intervention strategies to be tested include antiviral therapy late in gestation and boosting the immune system of newborns with gamma globulin.— A second area of this project which will be expanded in FY 1991 will be to follow up on the preliminary observation that mothers who transmitted HIV to full-term babies had very low or absent antibody reactivities to gp120. Mothers of uninfected full-term infants appear to confer immunologic protection against HIV-1 infection of their offspring via a high-affinity antibody to a gp120 epitope. Expansion of the laboratory component of this study would provide further information on the specificity of this epitope, which has clear relevance for vaccine development and perhaps perinatal immunotherapy.

A second project involves a study of cancer risk in HIV-positive mothers and their offspring. This project would involve establishment of a serum/cell repository for HIV-positive mothers and their offspring, as well as a registry for long-term follow-up of both mother and child. The tumor incidence (in particular lymphoma and Kaposi sarcoma (KS)) and latency will be determined in mothers and their children, and the presence of the repository will make it possible to evaluate retrospectively cancer risk as related to serum antibody status and coinfection with other viruses.

Another project, designed to determine the influence of major histocompatibility genes and gene products on disease progression in individuals infected with HIV-1 during the perinatal period, will be expanded in FY 1991. HLA typing will be performed at birth and the children will be followed prospectively for progression to diseases (KS, lymphoma and opportunistic infection) associated with HIV seropositivity. So far, more than 80 HIV-1 seropositive individuals in a hemophilic sibling pair study have been HLA typed and analyzed for disease progression as related to HLA haplotype. Preliminary results indicate that in siblings where one individual developed AIDS, that individual's HLA haplotype was different from other infected siblings without the disease. In other siblings concordant manifestations of disease progression (not AIDS) was associated with shared HLA haplotypes.

OBSTACLES TO CLINICAL TRIAL ENROLLMENT

Mr. Early. I understand that there is a growing reluctance on the part of private third-party payers to provide reimbursement for the non-research clinical care costs of cancer clinical trials. What effect is this having on clinical trials and what steps is NCI taking to address this problem?

Dr. Broder. Third party payers, including the Health Care Financing Administration (HCFA), Blue Cross/Blue Shield, and other private insurers have become increasingly reluctant over the past several years to reimburse hospitals and patients for the costs of the non-research, routine medical care that is administered in the setting of cancer clinical trials. While NCI-sponsored clinical trials may involve experimental therapy in the technical sense, they are really providing state-of-the-art treatment. Already these policies are slowing accrual to some NCI-sponsored Phase I and II studies and, if continued, they could significantly decrease the pace of clinical progress in our country.

NCI has undertaken several programs to educate patients and the general public about the importance and benefits of participating in clinical trials. Practicing community oncologists are working to educate citizens about various insurers and their policies regarding coverage of investigational and off-label cancer therapies. Our network of community clinical oncology program units is very important in this regard. In the long run, efforts to involve the consumer in the negotiations with private insurers will be an important part of solving this problem.

The formation of a committee to guide decision-making about reimbursement for investigational therapies has been a focus of discussion at the ongoing proceedings of the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS (the Lasagna Committee). This committee is chaired by Dr. Louis Lasagna and was constituted by the President's Cancer Panel at the request of then Vice President George Bush. Such a committee may make recommendations regarding which investigational therapies for which diseases are worthy of third-party reimbursement and might seek to bring a consensus to such decisions. The Lasagna Committee's report to the President's Cancer Panel with their final recommendations is expected in the Spring of 1990.

CLINICAL TRIALS ACCRUAL

Mr. Early. I understand that in an effort to improve accrual (enrollment) in clinical trials and to speed completion of these studies, NCI has initiated a program of supplemental funding use?

Dr. Broder. Several programs aimed at increasing accrual have been given priority funding in order to speed the completion of important clinical trials. The High Priority Trials program and the Cooperative Group Oncology Program activity are aimed at increasing patient accrual in studies judged to be of preeminent importance. In addition, great emphasis is being placed on the recruitment of minority cancer patients to clinical studies. Through Minority Satellite Supplements, Clinical Cooperative Groups are provided additional funding on a per capita basis for accrual of minority patients. The Minority Satellite Supplement Program is being linked to a new initiative to foster greater access of racial minorities to clinical cooperative trials.

Cancer centers also contribute to patient accrual in two main ways as they fulfill their responsibility for community service and outreach. Cancer centers are active participants in the Cooperative Groups and provide a significant number of patients entered onto these studies. This relationship benefits all parties involved since patients can access innovative therapies through a cancer center without having to travel great distances and the clinical investigators are able to complete a trial in a more timely fashion and determine if the investigational therapy represents a significant therapeutic advance. Cancer centers that are also members of Cooperative Groups can increase outreach efforts to the socioeconomically disadvantaged members of their community through Minority Satellite Supplements.

Mr. Early. Does this mean clinical trials may not be adequately funded to begin with?

Dr. Broder. Trials are funded adequately, given the total availability. However, there are substantially more important scientific hypotheses and promising new treatments than can be accommodated in the current clinical trials system. Only about

31,000 out of a potential 1,000,000 new patients participate in clinical studies each year. With the explosive increase in new drugs, biologicals (including interleukins, growth factors, and monoclonal antibodies), new radiation techniques, etc., the current clinical trials program could be doubled in size without exhausting the available (promising) options. In FY 1991 it is estimated that 34 new clinical trials will go unfunded.

ADDITIONAL FUNDS

Mr. Early. If an increase over the FY 91 request is provided, how would you use these additional funds?

Dr. Broder. Should additional funds over the 1991 President's Budget be provided, they would be allocated around the cornerstones of the National Cancer Institute -- basic research, prevention and therapeutic trials, and cancer centers. We would try to maximize the research opportunities available today through a careful balancing of program needs. Each of the mechanisms of support have been developed with a particular objective in mind and to meet a specific need. It is important to the total national program that this balancing be flexible in order to adjust to emerging, unanticipated opportunities.

More specifically, and dependent on the amount of additional funds, research project grants would be increased to permit funding both the non-competing and competing awards at closer to peer-reviewed recommended amounts. Cancer centers would be increased in order to avert the potential necessity to phase out several of the ongoing centers and to fund closer to their full recommended amounts.

Cancer information dissemination, including activities directed towards minority, rural and underserved populations will be expanded and given a high priority. Clinical trials, both therapeutic and prevention, would be augmented as would research investigating the potential of a vaccine for cancer.

Grants to funds facility needs, which have not been available to the NCI for award to institutions throughout the country since 1987, would be provided a portion of any increase over the President's Budget. The total National Cancer Program requires a constant infusion of investigators into the field. To that end, additional funding would be provided for training and education activities including National Research Service Awards and the Cancer Education Program. Given the changes that are evolving throughout eastern Europe, international initiatives emphasizing training, clinical trials, basic research and information dissemination would be given a priority.

Mr. Early. How much has been allocated for the Community Clinical Oncology Program in FY 1990 and FY 1991?

Dr. Broder. NCI estimates approximately $13 million will be spent on the Community Clinical Oncology Program for both FY 1990 and 1991. This program is an important component of our technology transfer initiatives (i.e., the latest research advances are transferred to the public).

INTERNATIONAL ACTIVITIES

Mr. Early. Doctor, a lot has changed in Eastern Europe and Russia during the past six months. What has the NCI done in response to these new opportunities?

Dr. Broder. Within NCI, the Office of International Activities works to further scientific collaboration between the United States and other countries. This office provides assistance to visiting scholars, sets up joint scientific programs, and works with international organizations. Within another component of NCI, the International Cancer Research Databank Branch (ICRDB) utilizes state-of-the-art technology to amass, organize, and disseminate research data. The NCI actively promotes this exchange of data worldwide among cancer researchers and practicing physicians. Looking specifically at Eastern Europe and Russia, we see more collaboration taking place; expectations are high that communication regarding cancer research will continue to grow more open.

Collaboration in cancer research with the USSR has expanded dramatically. The Soviet coordinator for the U.S.-Soviet bilateral program has proposed many more visits of Soviet cancer researchers to American laboratories. In addition, the Soviet government now permits their scientists to visit U.S. laboratories for longer periods of time. I have met with Soviet Ambassador Dubinin, and he is most interested in fostering these relationships.

The All-Union Cancer Research Center (AUCRC) in Moscow is conducting clinical trials in parallel to some being conducted here. A treatment protocol using cisplatin in testicular cancer has nearly achieved full patient accrual and three additional protocols dealing with colon and breast cancer were started last year. Working in collaboration with these studies, an NCI investigator has just returned from a two-month visit to Moscow.

In an epidemiological project, NCI scientists will collaborate with researchers in Moscow in developing probes for the early detection of pancreatic carcinoma. Because of the poor prognosis of pancreatic patients at all stages, any hope of successful treatment is dependent upon a very early diagnosis, coupled with newer therapeutic modalities and treatment options. Much of the clinical technology available for the identification of pancreatic cancer is based upon antigen recognition by a variety of monoclonal antibodies. However, a major difficulty with many of the monoclonal antibody assays is the presence of these antigens in a normal pancreas and in benign pancreatic disease. In this collaborative effort, NCI scientists and their Russian colleagues will look selectively for minor species of messengers in variously-staged pancreatic tumor material in order to clone and molecularly characterize these species for utilization as diagnostic markers.

An American delegation of prominent cancer researchers will be visiting Moscow this March to assess the progress of these treatment and epidemiological studies. The Soviet Union has traditionally shown excellence in mathematics and physics research. We are exploring appropriate cancer-related collaborations in such areas of excellence.

Preliminary discussions are underway to explore the feasibility of establishing two U.S.-Soviet cancer institutions, one in Moscow and one in the Soviet Far East. The NCI is prepared to assist the Soviets in the training of their future scientific and clinical faculty. Long-term training of Soviet scientists in the West will acquaint them with newer techniques which should translate into more use of state-of-the-art treatment regimens and foster further collaboration. In addition, Soviet researchers have expressed interest in products manufactured by U.S. biotechnology and pharmaceutical industries, and in American publications related to cancer research, treatment, and prevention.

Poland and Hungary have had active bilateral cancer programs with the U.S. during the last decade. A U.S.-Hungarian workshop was held last fall in Budapest to evaluate the 10 year-old program. Its continuation was endorsed, and the Polish and Hungarian coordinators for the programs have enthusiastically responded to NCI's initiative to provide them with the PDQ and CANCERLIT databases.

Additionally, there are several areas in cancer etiology research, both basic laboratory research and epidemiologic studies, which could be expanded or initiated with Eastern European scientists. For example, NCI scientists and their counterparts at the Maria Skjlodowska-Curie Memorial Institute in Poland will soon initiate a biochemical epidemiology project in Silesia. Silesia is a major industrial center in Poland, and iron and steel production and coking operations have led to extremely high levels of polycyclic aromatic hydrocarbon (PAH) and other contaminants in air, soil and water. Some occupations, particularly coke oven operation, further contribute to PAH exposure. Therefore, this region will be a unique resource for the study of human environmental carcinogenesis in terms of markers of exposure, DNA damage and repair, and adduct formation. Another collaborative project in cancer epidemiology is ready to be initiated with scientists in Hungary. Stomach cancer is still the leading type of cancer in much of Eastern Europe. Recent reports from Hungary indicate that the incidence there is particularly high. The causes of stomach cancer are not well understood; however the decreasing incidence in various other parts of the world suggest that it is largely a preventable disease. This epidemiology project in a high risk area such as Hungary will complement ongoing NCI investigations of stomach cancer in China and Italy and could provide information on dietary and other risk factors which would be useful in planning prevention strategies.

In other Eastern European nations, the most dramatic changes are taking place in our relations with cancer research institutions in East Germany, Czechoslovakia, and Yugoslavia. Very few contacts were permissible in the past between cancer research scientists from these nations and their American counterparts. The first scientific exchanges with NCI and other U.S. laboratories have now been scheduled for this spring.

It is likely that a number of possible new initiatives dealing with cancer information and Eastern Europe will be the topic of a President's Cancer Panel meeting in the fall of this year.

ACCOMPLISHMENTS

Mr. Early. The Nation has invested considerable funding for cancer research over the years. Gains have been shown in many areas over the past few years. Briefly, Doctor, can you give me the top three or four accomplishments of the past year?

Dr. Broder. As you know, cancer is a complex, diverse, and formidable disease and yet we have effective treatments and marked improvements in cancer mortality in young children and in adults under age 65. This year lung cancer mortality rates dropped from the mid-1970s to the mid-1980s -- a dramatic 29 percent drop in white men aged 35 to 44 -- and experts predict they will continue to drop -- this is believed to be the payoff of the basic research linking smoking to cancer and the subsequent public education campaigns on smoking cessation and prevention.

Past and future progress in preventing and curing cancer are predicated on a broad base of biomedical research. This has been a year of high scientific achievement in cancer research.

To illustrate: two NCI scientists working with colleagues from the National Heart, Lung, and Blood Institute made medical history by inserting new genetic material into human cells in the laboratory and then placing the cells back into a patient. They were then able to track the presence of genetically engineered cells in the patient's circulatory system for several months. These experiments built on previous NCI research on natural biological elements within the body that fight cancer. As a result, we are now on the threshold of new gene therapies to correct or replace missing or damaged genes that cause devastating illnesses -- such as severe childhood immune deficiency.

NCI also filed Investigational New Drug (IND) applications for eight drugs and 11 new biological response modifiers -- many for previously untreatable cancers or AIDS. Recently, NCI-supported scientists have made a number of important genetic discoveries. In particular, there have been new insights into the role of tumor suppressor genes. The NCI-Navy Medical Oncology Branch has found that certain genetic abnormalities play an important role in the genetic events that culminate in lung cancer. An NCI-grantee at Johns Hopkins has shown that an accumulation of complex genetic alterations is associated with the progression of colorectal tumors from benign adenomatous polyps to frank carcinomas. This lays the groundwork for new advances in the early diagnosis and treatment of colorectal tumors.

Other genetic findings include the location of the gene for familial malignant melanoma on chromosome 1. About 10 percent of all malignant melanoma cases fall into this category. Five proteins involved in metastasis, the wild spread of cancer from the original tumor, have been identified. These proteins may be involved in positive and negative regulation of tumor invasion and metastasis and include the laminin receptor, autocrine motility factor, NM23 metastasis suppressor protein, type IV collagenase, and the newest discovery TIMP-2 metalloproteinase inhibitor. These discoveries add to the knowledge needed to control this often lethal process.

NCI-supported research is developing new adjuvant therapies. These employ the use of chemotherapy or hormonal therapy after surgery. This year NCI-supported scientists showed that deaths from a type of advanced colon cancer could be reduced a third, using an adjuvant treatment combination of levamisole, an immune stimulant and 5-fluorouracil (5-FU) in treating Dukes' C colon cancer. There will be approximately 110,000 new cases of colon cancer in 1990 and 21,000 will be the Dukes' C stage.

NCI-supported studies showed that many women with node-negative breast cancer could benefit from chemotherapy or hormonal therapy after surgery. About 70,000 of the 142,000 women who are diagnosed each year with invasive breast cancer may benefit from this treatment advance. Clinicians have known that up to 30 percent or more of node-negative patients ultimately have recurrences of their cancer and often die of these recurrences. These adjuvant therapies can significantly reduce the rate of recurrence and hopefully will not only give them disease-free years, but also extend their lives.

Currently there are promising adjuvant therapies being developed for patients with bladder, head and neck cancers.

A number of new diagnostic tests which measure tumor secretions, oncogenes or DNA, help identify the breast cancer patients who can most benefit from specific treatments. These tests come directly from basic cancer research and have been quickly developed to help patients.

Other basic research discoveries, such as the finding that the N-myc oncogene is amplified in the neuroblastomas of pediatric patients and that the HER-2neu oncogene has been confirmed not only in breast cancer, but also in ovarian cancer, are the basis of new diagnostic and prognostic tests.

In addition to the INDs mentioned above, new combinations or new uses of old drugs are being developed. Recent research at the NCI-funded cancer center at the University of Arizona demonstrated that adding verapamil, a calcium channel blocker used in cardiology, to the usual chemotherapy regimen helped to reduce drug resistance in patients with refractory myeloma and non-Hodgkin's lymphoma.

NCI-supported cancer centers play a vital role in not only the basic research, but the clinical trials needed to develop new treatments and approaches and in bringing the best of new cancer treatment to their communities. The cancer centers provide an important resource in identifying regional cancer problems and focused research, prevention and treatment to aid their areas.

NCI has reached out to help people deal with cancer. The Cancer Information Service, reachable by a toll-free 1-800-4-CANCER number, answered over 500,000 questions. The Physicians Data Query, a computerized database, provided state-of-the-art information to physicians and referred tens of thousands to NCI-supported clinical trials where patients could receive experimental or state-of-the-art cancer treatment. Over 500,000 patient education brochures were mailed to give cancer prevention or screening information or to help patients understand cancer, cancer treatment and to help them in dealing with side effects and other aspects of their treatments.

Turning to achievements in AIDS research and in related areas of cancer, NCI-supported scientists have identified new families of viruses, such as the human retroviruses involved in AIDS and some leukemias. In addition, we know more about the human papilloma virus and its attack on suppressor cells as they affect the development of cervical cancer. The long-term commitment of NCI to the study of viruses has contributed to its success in preventing and treating AIDS. The value of this research extends beyond cancer as such viruses are involved in certain chronic liver and neurologic diseases.

NCI-supported scientists are making important contributions in AIDS drug and vaccine development. NCI is taking the lead in the development of treatments for children with AIDS.

Combining physics and math, scientists have constructed a three-dimensional model of the crystal structure of the HIV-1 protease using the supercomputer at the NCI's Frederick Cancer Research Facility. Knowing the exact structure of this important molecule will allow for the design of a molecule to block the reproduction of the AIDS virus.

Recently scientists at NCI's Frederick Cancer Research Facility have completed important steps in the development of a vaccine for AIDS. Among these steps has been the identification of target sites on the HIV envelope protein that are most effective in eliciting an immune response which will help with the development of a vaccine. Other approaches have included altering genes in the HIV virus to make it impossible for the virus to reproduce.

FLUORIDE

Mr. Early. Recently, news accounts have reported a potential influence of fluoride on the health of the American people. What can you tell us about the carcinogenic potential of fluoride in the drinking water?

Dr. Broder. We treat all such reports seriously, and will respond with facts and informed opinion as quickly as possible. A recent National Toxicology Program (NTP) study (as yet not peer-reviewed) of sodium fluoride in F344/N rats and B6C3FI mice of both sexes gave some evidence of osteosarcomas developing in male rats at the intermediate dose of 45 ppm (as fluoride), 1/50; and at the highest dose 79 ppm (as fluoride), 4/80; none at 25 ppm and none in the controls.

The NCI previously studied and published (*Journal of the National Cancer Institute* 57: 757, 1976) a study on cancer mortality and incidence statistics for U.S. counties 1950 to 1969. No trends for any form of cancer, including bone cancer, could be ascribed to the consumption of water that is artificially or naturally fluoridated. It is worth emphasizing that in several areas of the country, drinking water is fluoridated by nature. Several other studies (a total of 21) in the U.S. and abroad, especially in Great Britain, are remarkably consistent in finding no evidence of overall or site-specific excesses of cancer that could be attributed to the level of fluoride in drinking water. This led to the conclusion that "variations geographically and in time in the fluoride content of water supplies provide no evidence of an association between fluoride ingestion and mortality from cancer in humans." We currently have no reason to doubt this conclusion. A few potential disadvantages of the available data should be noted, however. All are descriptive studies based on geographic comparisons. While they are strong studies because of the widespread and often abrupt changes in fluoride exposure, they are nevertheless still based on correlational analyses that are subject to inherent limitations. Secondly, only one other study from England, in addition to the NCI study, included an evaluation of *incidence* as well as *mortality* data. While this is not a drawback for the evaluation of most sites, it is a possible concern for bone cancer (suspected on the basis of bioassay data), since this tumor may be theoretically misclassified as a cause of death because of the frequency of bone metastases from a variety of primary malignancies.

The NCI has recently made an examination of time trends in osteosarcomas from the Third National Cancer Survey (1969 to 1971) and the Surveillance, Epidemiology and End Results (SEER) program for the five geographic areas that were common to both surveys. By the end of 1969, the vast majority of the population covered by these five areas was drinking fluoridated water. Statistically speaking, these rates do not appear to be rising over this time period, and an analysis of age-specific patterns is now underway through 1987. Two further analyses are planned. First, the NCI will update its 1976 mortality study with data available now from the 1970s and early 1980s. Second, colleagues from the National Institute of Dental Research and Centers for Disease Control have agreed to provide NCI with the fluoridation status of the geographic regions covered by the SEER areas, at the county level. When these data are in hand, the NCI will determine whether any meaningful epidemiologic comparisons are possible with the incidence data as can be carried out with the mortality statistics. The NCI hopes to have all analyses completed by June 1990.

MORTALITY RATES FOR RICH AND POOR AMERICANS

Mr. Dwyer. Last year, the American Cancer Society embarked on a program to improve the cancer survival rate for poor Americans, including minorities.

What can you tell us of the mortality rates of "rich" and "poor" Americans from cancer?

Dr. Broder. There is no question about the effect of poverty on differential rates of cancer incidence, mortality, and survival. A recent study measures the contribution of socioeconomic (SES) factors to the observed difference in cancer incidence between Blacks and whites. As a measure of socioeconomic status the study used census tract levels of median family income, percent of families below the poverty level and years of education. Twelve cancer sites were studied; in eight of these sites Blacks have a higher risk than whites. Of the three SES variables, percent of families below the poverty level was shown to have the strongest effect on incidence and to have an effect almost equal to all three SES variables combined. When site specific cancer incidence rates were adjusted for age and sex, and with and without this poverty variable, the poverty variable was shown to explain a large proportion of the race differential in cancer of the breast, cervix (in-situ and invasive), esophagus, male lung, pancreas and stomach. The poverty variable had little or no explanatory power in cancer of the colon, rectum, uterine corpus, bladder, prostate and multiple myeloma.

SES determinants of survival have been little studied, but most published studies have shown an inverse relationship between SES and survival, given stage at diagnosis. For example, a study of multiple myeloma patients in two New York hospitals found in a multi-variate regression analysis of 144 patients that the most significant prognostic factors were hypoalbuminemia (low albumin in the blood) and a census-tract measure of household overcrowding (families with more than 1.5 persons per room), which is highly correlated with poverty. Race was not a statistically significant independent prognostic factor. It is striking that a census-track measure of poverty can predict bad outcomes in cancer.

Income and health insurance coverage (which is inversely related to income) have also been shown to be determinants of who gets screened for early detection of cancer. Data from a nationwide telephone survey of 4,659 women has shown that income has a statistically significant positive relationship to receiving a Pap smear, and the absence of health insurance was shown to have a statistically significantly inverse relationship to receiving both a Pap smear and mammography.

In another study reports that patients with non-small-cell lung cancer are more likely to be treated with surgery or receive radiation or chemotherapy if they are covered by private medical insurance.

The National Cancer Institute will be releasing a Request for Applications (RFA) this year, and this has the goal of reducing cancer incidence and mortality and improving cancer survival rates for minority and underserved persons who are typified as low income/education and are high-risk populations. The focus of this initiative will be on determining how to meet the full spectrum of cancer needs for those segments of our population at the extreme in terms of excess risk of cancer mortality and morbidity. The Institute has a full range of ongoing prevention and early diagnosis programs targeted at people who are poor. Also, cancer centers which are designated as comprehensive carry on a number of community service and outreach activities in their communities, and these will have an impact on poverty-related cancer statistics.

TARGETING PREVENTION PROGRAMS

Mr. Dwyer. Do you believe that cancer prevention programs and information could be better targeted toward poor whites and minorities?

Dr. Broder. Most definitely, and NCI is working to do that. The Office of Cancer Communications is developing and testing materials that should effectively reach low-income, low-literacy populations. In communications campaigns, NCI is also utilizing spokespersons and working through intermediary organizations that can best reach the minority community. NCI recognizes the disparate cancer mortality rates of lower income Americans and minorities and is committed to reaching those audiences with targeted messages through appropriate channels to inform them of the importance of early detection, prevention, and treatment. We aim to serve the needs of poor whites, Blacks, Hispanics, Native Americans, and Native Hawaiians.

Cancer prevention and control research initiatives have been implemented by the Special Populations Studies Branch at NCI with the expressed purpose of improving the health status of minority and underserved populations which include the poor. However, these populations have special barriers which must be overcome before the full value of cancer prevention and control knowledge can be realized among these high-risk groups. These barriers include: low educational attainment, which results in a lack of understanding the medical care system and the value of preventive measures; low income which reduces purchasing power for food and preventive medical care; having a language other than English as the primary language in the home; and living and working in high risk environments. These barriers are formidable, but, we believe they can be overcome and lead to an improvement in the overall health of underserved Americans. We have special programs aimed at reaching Americans over 65; a population with disproportionate poverty factors.

This year's Minority Cancer Awareness Week activities will focus on early detection activities for Black and Hispanic Americans. NCI's Office of Cancer Communications and the National Black Leadership Initiative are working with minority media and intermediary groups to promote the early detection of breast, cervical, and prostate cancers as well as smoking cessation. Public service announcements, a video news release, and specially developed materials (including Spanish language materials) have been developed and disseminated for this promotion.

The outreach capabilities of the regional CIS offices have now been expanded to include the placement of a health educator in each of these local offices. This individual will be responsible for identifying the specific target populations in their service area and tailoring national programs to the specific need of such populations. Specifically this will include efforts to reach large Black and Hispanic populations in New York City, Illinois, Texas, Louisiana, Ohio, Alabama, North Carolina, California, Pennsylvania, Florida and New Mexico. In addition a new emphasis has been placed on reaching low income and illiterate populations. Local offices serving Ohio, Kentucky, Tennessee, West Virginia and North and South Carolina will adapt materials and programs to reach these audiences. These program efforts will be coordinated by a Special Populations Task Force and will work to identify appropriate strategies and methodologies for reaching these populations.

INSURANCE PAYMENT DENIAL FOR BREAST CANCER DRUG TREATMENT

Mr. Dwyer. Dr. Broder, much as been made about the importance of drugs and other adjuvant therapies, in addition to surgery, for women who have breast cancer.

Despite the apparent success of adjuvant therapy, some insurance companies are denying payment for breast cancer drug treatments, questioning the efficacy of this approach. Do you believe that these insurers are raising legitimate concerns about patient safety or are merely looking for ways to reduce their costs?

Dr. Broder. We are currently exploring the magnitude of the problems with reimbursement for breast cancer drug treatments. A survey aimed at documenting problems with reimbursement has been sponsored by the American Society of Clinical Oncology and the NCI; data are still being collected. We know that expensive and complex technologies such as bone marrow transplantation, and Interleukin-2/LAK therapy are subjected to close scrutiny by insurers. There is some anecdotal evidence of disapproval of such claims. Meetings between the NCI and representatives of the insurance industry have been held to explore the complex problem of identifying effective therapy and providing it in an economically feasible way. A special subcommittee of the President's Cancer Panel is reviewing these issues.

BREAST CANCER EDUCATION

Mr. Dwyer. What is NCI doing to educate doctors, patients, and insurers of the need for drugs, as well as surgery, to treat breast cancer?

Dr. Broder. The NCI's information dissemination programs are designed to promote and give easy access to the latest information available for cancer treatment, early detection, and prevention; information related to breast cancer is integral to these programs. Through the Office of Cancer Communications, NCI continually updates breast cancer patient education publications to reflect state-of-the-art diagnosis and treatment, and publicizes several clinical trials involving breast cancer as being national high-priority trials.

To directly serve the health professional community, NCI several years ago developed the Physician's Data Query (PDQ) system. This system provides on-line access to data bases which include up-to-date information on all types of cancer treatments, both standard and experimental, and maintains a national directory of practicing oncologists. The data available through PDQ, including information on breast cancer, is continually updated and evaluated to ensure that it is accurate and current. PDQ is easily accessible to physicians either directly through use of a modem-equipped computer, or through an intermediary service which would access PDQ on behalf of many physicians. Insurers have access to the information on this system, as well to the cancer-related information published in medical journals, including the Journal of the National Cancer Institute (JNCI).

The Institute's Cancer Information Service (CIS) responds to over 450,000 inquiries each year from the general public, including health professionals; breast cancer has accounted for approximately 25 percent of all inquiries. The CIS utilizes PDQ to ensure that it can respond to callers with the most accurate cancer information. The CIS also uses PDQ to provide callers with referrals to clinical trials evaluating new treatments, including breast cancer studies.

When the National Cancer Institute mailed its Clinical Alert on Breast Cancer in May 1988 to 13,000 physicians, and made concurrent announcements to the press, the CIS experienced a 30 percent increase in the number of calls on breast cancer. Callers included patients (39 percent), family members of patients (16 percent), health professionals (five percent) and the general public (25 percent). These callers requested information on the new considerations for the treatment of node-negative patients with drugs or hormonal therapy after surgery, and sought referrals to clinical trials. A follow-up assessment of this alert by physicians drew a notable number of responses; the majority of the responding physicians said they changed their treatment practice as a result of the alert.

And, through NCI's Community Clinical Oncology Program, physicians practicing in community settings have access to NCI-approved clinical trials, which represent state-of-the-art cancer management. Among these are several high-priority protocols specifically addressing treatment options for breast cancer. Through this mechanism, community physicians are educated about the most up-to-date use of drugs and surgery in the treatment of breast cancer.

At the current time, NCI has established a network of intervention studies among women residing in various communities in seven states designed to improve the utilization of mammography, clinical breast exam, and breast self-examination. In 1988, 6,900 women living in these areas were surveyed on the utilization and barriers or hindrances to breast cancer screening.

The interventions are targeting approximately the 220,000 women aged 50 and over and the physicians in these communities. This important effort will determine the most effective health promotion strategies to increase breast cancer screening in older women and should have for reaching implications for the reduction of breast cancer mortality.

Last year, NCI began the National Breast Cancer Screening Campaign to 1) encourage women in the appropriate age groups to obtain mammograms and 2) urge physicians to recommend mammograms to their patients. In cooperation, the NCI and the Susan G. Komen Foundation chaired by Nancy Brinker, convened the Women's Leadership Summit on Mammography to launch this education campaign. This Capitol Hill event drew upon and elicited the support of nationally-recognized women leaders to increase awareness of the importance of mammograms by taking the mammography message to their constituencies directly, and to put mammography on their professional agendas for 1990 and beyond.

DRUG LABELLING PROCEDURES

Mr. Dwyer. Is the NCI working with the FDA to improve the drug labelling procedure to allow drug companies to more easily update their labels to reflect changes in usage.

Dr. Broder. Yes, NCI and FDA are working together to expedite the drug approval process for initial labelling as well as for supplemental labelling. NCI and FDA are collaborating to speed up the process of initial New Drug Application (NDA) approval by clearly defining what constitutes efficacy for various tumor types and by identifying new agents whose development is flagging, and designing intervention strategies. Clearly defining efficacy endpoints and communicating these early on to pharmaceutical firms will help not only the initial NDA approval, but supplemental NDA approval (updated labels listing additional indications) as well. NCI and FDA hold monthly Working Group meetings to discuss both overall policy and regulatory guidelines as well as specifics about particular new drugs and biologics.

The National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS, formed by the President's Cancer Panel at the request of then Vice President George Bush, and chaired by Louis Lasagna, M.D., has been conducting public hearings over the past year regarding ways to expedite the drug approval process. This Committee has heard from various interested parties including the pharmaceutical industry, FDA, NCI, drug development consultants and patient and health care advocates about ways to speed NDA approval including supplemental NDAs, the latter aimed at expanding the labelled indications for a drug. Several groups suggested that mandatory reasonable review periods be imposed for the examination of supplemental NDAs by FDA. Others suggested that parts of the NDA or supplemental NDA review could be contracted out to experts to assist FDA, leaving the final decision about approval in the hands of FDA. The Lasagna Committee is currently writing their recommendations and NCI anticipates that there will be specific ideas advanced about how to expedite these processes by summer. NCI and FDA will continue to work together to evaluate and implement these recommendations.

CANCER CENTERS

Mr. Dwyer. I have received correspondence from the Association of American Cancer Institutes which alleges that the budget request for cancer centers was altered by someone in the Administration after the body of the text had been written. What was the level of funding requested in the initial budget justification?

Dr. Broder. In its budget request to the Director, NIH, the NCI requested $144 million for cancer centers. This funding level would restore funds for centers phased-out in 1989 and 1990, which are expected to resubmit in FY 1991; pay continuing centers at committed levels and competing centers at recommended levels; approximately five new centers would have been added to support targeted programs focusing on prevention, clinical trials, minority demonstration, the populace over age 65, and the underserved. I am not aware of any specific alteration of the text that was submitted.

Mr. Dwyer. If Congress enacts the funding level requested for the cancer centers, $104.588 million, how many cancer centers would be in danger of losing funding?

Dr. Broder. With a cancer centers budget of $103 million, NCI may have to phase-out three to four existing cancer centers. Most experts have advised NCI that we should avoid significant downward negotiations, even to the extent that it may necessitate that some centers be phased-out. It is believed that reductions below a certain point threaten the excellence of the individual centers and, therefore, the total portfolio.

Mr. Dwyer. How much money would it take to fund the cancer centers adequately?

Dr. Broder. NCI's professional judgment budget supports centers at $144 million in FY 1991. This level would allow for centers restoration, payment of recommended levels for both competing and noncompeting centers, and the payment of new centers. To fund the 56 centers requested in the budget in FY 1991 at recommended levels, including the reductions taken in 1990, would require an additional $11 million.

CANCER CENTERS

Mr. Hoyer. If the Administration's cancer center budget is agreed to, how many cancer center programs would lose funding, or if the number of centers is maintained what percentage downward negotiation would result?

Dr. Broder. NCI is currently exploring ways to ensure that scientific excellence continues within the centers program while negotiating reductions from the peer-reviewed recommended funding levels for competing centers, or our commitment levels for noncompeting centers. If we are faced with the challenge of severe reductions from recommended levels, we would reluctantly reduce the numbers of centers supported. If in 1991, we maintain the 56 centers reflected in the budget, we would have to reduce competing centers by approximately 20 percent; noncompeting centers would be paid at commitment levels.

Mr. Hoyer. What, in your professional judgement is necessary to assure an appropriate level of funding and stability for the centers program?

Dr. Broder. NCI's professional judgment budget for centers in 1991 is $144 million. This level would allow for centers to be paid at peer-reviewed recommended levels, would restore centers phased-out in 1989 and 1990, and would allow for centers expansion by adding approximately five new centers throughout the country.

WOMEN IN RESEARCH

Mr. Hoyer. The NIH has a policy that encourages the inclusion of women in clinical trials, and the GAO is currently studying this issue.

I wondered if you had any data on whether women are adequately represented in extramural and intramural research supported by the NCI, and what steps should be taken if any to improve the situation?

Dr. Broder. The most important factor determining enrollment of any patient onto a clinical trial sponsored by NCI is the patient's eligibility for that trial. Eligibility criteria encompass the following considerations:

- Verification that the patient have the appropriate type and stage of cancer for that particular study;

- Absence of any other medical condition that would impair the ability of the patient to tolerate the proposed treatment or impair the investigator's ability to evaluate the results of that treatment, and

- The ability of the patient to understand and comply with treatment and followup provisions of that study.

There is no gender bias implied or stated in any NCI protocol. Obviously, clinical trials involving diseases particular to one sex or the other such as testicular or ovarian cancer, are restricted to patients of the appropriate sex. For diseases which affect both men and women, patients of both sexes are included in the clinical trial.

Gender is one of many variables that is analyzed with the results of a clinical trial. In some situations, gender has turned out to be an important criteria in evaluating the benefit from therapy. For instance, NCI has reported that women who are diagnosed with small cell lung cancer survive longer than men with the same diagnosis who are given the same treatment. The reasons underlying these sex-specific observations are unclear at present, but may be related to hormonal factors or to influences that have yet to be defined. Alternatively, sometimes such findings are due to random factors and are not real.

There has been a consistent policy to insure that women's participation in therapeutic studies has been optimized. This has been accomplished in two ways:

1) Intensive study of diseases that uniquely affect women. There are special organizations such as the Gynecologic Oncology Group (studying cervical, ovarian, and endometrial cancer) and the National Surgical Adjuvant Breast Project (studying breast cancer) dedicated to these diseases. Moreover four other Groups have protocols for breast and/or gynecologic cancer. Thus six of the 10 DCT supported Groups address women's diseases. More than 570 patients with gynecologic cancer and 3,000 breast cancer patients are entered on studies each year.

2) Full and complete access to studies which affect both men and women. For both pediatric and adult patients slightly more than half of all new cancer patients available for studies are women.

In the area of cancer prevention and control there has been a major emphasis on prevention and early detection of breast and cervical cancer. These studies range from research on the role of diet in reducing breast cancer to research on the best ways to encourage women to take advantage of mammography and Pap smears, two modalities shown to reduce mortality from breast and cervical cancer, respectively. Any current research that excludes women is directed toward specific occupational exposures or cancers in exclusively male organs.

UNDERSERVED POPULATIONS

Mr. Hoyer. The NCI plans expansion of the Surveillance Epidemiological and End Results Survey to add increasing numbers of Black and Hispanic Americans.

How will this help to reduce the disparity in cancer rates between minorities and the general population?

Dr. Broder. In 1973, the National Cancer Institute (NCI) initiated a population-based tumor registry reporting system for cancer incidence and survival. This system, the Surveillance, Epidemiology, and End Results (SEER) Program, receives data from five states (Connecticut, Hawaii, Iowa, New Mexico, Utah) and four metropolitan areas (Atlanta, Detroit, San Francisco/Oakland, Seattle/Puget Sound) representing approximately 10 percent of the U.S. Population. SEER data are used to assess the health burden of cancer, identify populations at increased risk, and measure the impact of cancer prevention and control efforts.

The SEER Program is an integral component of the NCI's Surveillance Program. In a 1988 review of the SEER/Surveillance Program, a panel of experts recommended that "The SEER Program should, in the interests of continuity, time series, and survival analysis, continue to collect incidence [and survival] data from the current registration areas. The registration areas should be expanded to achieve adequate coverage of those populations -- such as ethnic groups, rural dwellers, and the economically deprived -- that are not yet sufficiently represented."

At present, population coverage in SEER areas is as follows: 9.2 percent of U.S. whites, 8.3 percent of U.S. blacks, 8.6 percent of U.S. Hispanics, and 50 percent of other minorities (Chinese, Japanese, Filipino, Hawaiians, and American Indians). Hispanic subpopulations representing individuals of Puerto Rican, Cuban, and Central/South American origin, as well as Blacks living in rural areas, are underrepresented in our national cancer registry system (SEER). Usable incidence data for Hispanics are available from only one of the SEER registries (New Mexico), which effectively reduces representation from 8.6 percent to approximately four percent of the U.S. Hispanics.

Cancer reporting for minority populations is difficult. Race/ethnicity is not always reported in medical charts and cancer cases among these groups must be determined by indirect methods. Data for minority subpopulations are available only from the U.S. census that is conducted every 10 years. Thus, for years other than when the national census was conducted, estimates of cancer rates for minority populations must be extrapolated. Uncertainties are more pronounced for subgroups with significant migration patterns, particularly for local areas.

Because of the need for information on cancer rates in minorities, NCI will continue to seek cancer registries to join the SEER Program that can provide data of comparable quality to its other participants. Strengthening the Institute's cancer surveillance capability for minorities contributes to efforts which reduce the disparity in cancer rates between minorities and the general population. Specifically such data are used to:

- Develop and target new intervention strategies;

- Monitor progress of interventions, especially by use of incidence and survival data which are often more sensitive indicators than mortality of the effects of cancer prevention and control strategies;

- Educate public health agencies, practitioners, and health policy-makers about the cancer burden and provide a quantitative justification for prevention and control efforts; and

- Investigate the interrelationships among cancer risk factors, health behavior, and cancer outcome through special studies and linkage of data bases. For example, in collaboration with the Health Care Financing Administration, the NCI SEER database is being linked to data on cancer treatment and medical expenditures for Medicare beneficiaries to provide much needed information on the economics of cancer.

- Stimulate more basic research to resolve certain unexpected or unexplained trends. For example, prostatic cancer and multiple myeloma (a special cancer of the bone marrow) statistics and worsening in Black Americans. Several basic research approaches are now being directed to these problems.

Mr. Hoyer. Can you tell us the status of the request for applications on cancer prevention and clinical research in minority and other underserved populations?

Dr. Broder. The Request for Applications (RFA) entitled "Cancer Prevention and Clinical Research in Underserved Populations" will be released to the public in March, 1990, with a receipt date for applications of August 10, 1990. At the conclusion of the peer review process, it is anticipated that up to three five-year awards will be funded in FY 1991.

Mr. Hoyer. Can you outline your views on the level of access to state-of-the-art cancer diagnosis and treatment for Americans generally, as well as underserved populations?

Dr. Broder. The NCI represents a major investment by the American people for the general good of all the American people. For this reason, NCI will continue to focus on the problem of cancer in minority groups and other underserved populations. We want to ensure that the fruits of our research programs go to all Americans, rich or poor, Black or white, urban or rural, young or old.

It is well known that for several major cancers, most notably breast and cervical cancer, diagnosis at the earliest possible stage of disease provides the patient with the best opportunity for long-term survival. This suggests that the availability of state of the art technology for early detection should be as widespread as possible. Unfortunately, tests designed for the early detection of cancer are underutilized by large proportions of the population.

Clinical Breast Examination (CBE) by physicians is widely practiced and is about equally utilized among Blacks and whites. Lower rates for CBE are seen among Hispanics and among the elderly. These trends are more pronounced for mammography. Here, Black women are screened less frequently than whites, and Hispanics are screened least frequently. While there have been reports of a dramatic increase in mammography screening, there is still reason to believe that American women are not utilizing this technology to its fullest.

Unlike the mammogram, the Pap smear has gained broad acceptance throughout the population. Approximately 90 percent of women have had a Pap smear at some time, and about half of the female U.S. population had a Pap smear for screening purposes in the past year. Between 1973 and 1985, there was a significant increase in the number of Blacks and older white women who had recent Pap smears. The 1987 National Health Interview Survey data confirm that Black women are now more likely to be screened than white women. The 1987 data indicate that 75 percent of Black women and 70.8 percent of white women have had a Pap smear in the last three years. For Hispanics overall, the screening rate is 62.5 percent and for Hispanics who speak only or mostly Spanish, only 47.7 percent have been screened in the last three years. The screening rates still decrease with increasing age. Despite gains in certain groups, Pap smear screening has changed little since the early 1970s, leaving a significant minority of the population underserved. For screening tests, the patterns of less frequent use of cancer screening tests among Blacks and Hispanics appear when we examine digital rectal exams, fecal occult blood tests, and proctoscopy. The NCI is concerned that certain geographic regions (e.g., Kentucky and West Virginia) have high rates of cervical cancer and is a focus on better communication approaches to reach at risk populations.

Lower education and income are associated with less frequent use of tests, and in most cases help to explain racial differences in the use of cancer screening. Poverty, irrespective of race or ethnic background, is a risk factor for cancer.

A report from an evaluation of NCI's Community Clinical Oncology Program (CCOP), showed that for four of ten patterns of care cases examined among breast cancer patients, Blacks received less often state-of-the-art care than whites. It bears noting that in six patterns, there were no differences. Similar findings in differential treatment in bladder cancer patients were reported using the SEER database. Other studies show that there is a marked change in recommended treatment with increasing age: older cancer patients are more likely to receive no therapy than younger ones, even controlling for stage of disease and other covariates. A study in New Hampshire of lung cancer patients showed that a variety of socioeconomic factors, such as marital status, medical insurance coverage, and proximity to a cancer treatment center, were also related to type of treatment received. Finally, reports by the GAO have shown that there may be problems with the timely provision of state of art care using the NCI's SEER database.

Access to clinical trials is also a measure of receipt of state-of-the-art treatment. In general, there is limited participation in clinical trials research by Black, Hispanic, Asian-American, Native-American, and other minority cancer patients. During the first phase of NCI's Community Clinical Oncology Program (CCOP) only seven percent were minorities, compared with 13 percent minority representation in SEER and 20 percent in the U.S. as a whole.

Underserved populations have less than adequate access to quality cancer prevention and control services including primary and secondary prevention services, i.e., cancer risk reduction education, cancer screening and early detection, and treatment. These high-risk populations reportedly utilize preventive health care services less frequently than the general population and are reported to use emergency rooms and hospital outpatient departments as a primary source of care. Health care utilization patterns coupled with inaccurate knowledge of cancer preventive strategies, contribute to the poor cancer survival and mortality rates in these groups.

Underserved populations are at higher risk than the general U.S. population and also suffer disproportionately high rates for many health problems, i.e., AIDS, substance abuse, heart disease, diabetes, homicide and cancer.

While numerous factors may be associated with the indicators of poor health status experienced by the underserved, access and availability to medical care service for the underserved are clearly affected by lack of ability to pay for the services. Underserved populations lack adequate health insurance coverage; for example, a higher proportion of Blacks and families with low incomes are underserved -- 23 percent of Blacks under the age of 65 have no health insurance compared to 14 percent of comparable whites. Thirty-seven percent of the families with an income under $10,000 have no health insurance but less than four percent of families with an income over $35,000 have no health insurance.

Additionally, when cancer survival data are linked with the Census tract education and income data, strong survival gradients exist for several cancer sites. For example, the five-year relative survival rate for white college graduates with cancer is 57.5 percent, 47 percent higher than the rate of 39.2 percent for those whites not finishing high school. Among Blacks, the picture is similar, the five-year relative survival rate of 54.5 percent for college graduates is 65 percent higher than the rate for those who did not finish high school. The survival gradient patterns are virtually identical when stratified by income; however, the survival rates for whites in the upper income levels are greater than for Blacks in the upper income levels. Additionally, lower income whites have greater survival rates than do lower income Blacks.

Finally, in certain settings, women represent an underserved population. Since 1973, the death for female lung cancer has increased by over 100 percent. This increase is linked almost entirely to smoking practices. The NCI will try to do more regarding smoking as a women's health issue.

Mr. Hoyer. How much of the effort to improve access to existing diagnostic and treatment options should be focused on patients as consumers as compared to physician providers?

Dr. Broder. Research to date suggests that both physicians and women should be the focus of interventions to increase breast cancer screening rates. During the past three years, NCI has funded a network of breast cancer screening intervention studies to evaluate various health promotion strategies, including both physician and community women interventions. The studies that are currently underway in various communities in seven states (California, Massachusetts, New Jersey, New York, North Carolina, Pennsylvania, and Washington) have shown that low rates of screening mammography are due to a missed clinical opportunity, and that simple interventions by physicians could increase screening substantially. The two most common reasons women gave for never having had a mammogram were that they didn't know they needed it, and that their physician had not recommended it. In one area (Los Angeles), 80 percent of the women reported that they would definitely get a mammogram if their doctor recommended it. Women 50 to 64 years old were over four times more likely to have had a mammogram in the previous year if their physicians had discussed it with them. Thus, physician recommendation is potentially an important key to mammography referral, and should be given major attention in research.

We are currently testing the role of physician intermediary organization in promoting the NCI early detection guidelines in a program called "Prescribe for Health". Since primary care physicians play a central role in the diagnostic process, particularly for follow-up of positive diagnostic tests and treatment recommendations, considerable effort must be spent in encouraging this group to recommend cancer screening tests. This does not, however, preclude the funding of educational efforts specifically targeted towards women. The gap in knowledge about cancer screening tests for women must be eliminated so that recommendations by physicians for these tests will be followed.

NCI believes that it is important to provide ready access to existing diagnostic and treatment options for both patients and physicians. The Cancer Information Service provides up to the minute information on all aspects of cancer diagnosis, treatment and prevention to the American public via the toll-free number 1-800-4-CANCER. Physicians can avail themselves of the most current information about ongoing treatment protocols and their geographic location through the Physician's Data Query (PDQ) system. Through these important channels of information dissemination, NCI attempts to educate both the patient as well as their physicians about all available options for state-of-the-art cancer diagnosis and treatment.

CHEMOTHERAPY DOSAGE

Mr. Hoyer. One of the networks recently aired a segment on one of its news magazine broadcasts that indicated that many physicians may be reducing the dosages of therapeutic drugs in order to reduce some of the unpleasant toxic side effects of the anti-cancer drugs. The report indicated that such practices may reduce the chances of survival for many cancer patients.

Does NCI have any indication that this is occurring?

Dr. Broder. Oncologists have long been interested in the identification of factors which influence response to treatment and survival from cancer. Large scale analysis of a number of clinical trials has revealed that one of those factors is the dose-intensity of chemotherapy (i.e., the amount of chemotherapy delivered over a set period of time) for early stage and advanced breast cancer, ovarian cancer, colon cancer, and Hodgkin's and non-Hodgkin's lymphomas. This concept has not been universally accepted or applied in clinical practice and this is felt to contribute to inferior response rates and survival from lower dose, "less toxic" chemotherapy. It is becoming clear that dose intense chemotherapy, including bone marrow transplantation regimens, may be administered safely through the use of currently available supportive care measures and that many fears about dose intensive regimens are unfounded. However, while dose-intensity is important, it is not the only factor that determines whether a cancer can be cured. Some cancers develop drug resistance and grow despite good doses.

Mr. Hoyer. If so, how do we combat this practice?

Dr. Broder. It is difficult to obtain an accurate assessment of the extent of underdosing that occurs in cancer treatment, but the participation of many community physicians through NCI's Community Clinical Oncology Program and Cooperative Group Outreach Program, allows practicing oncologists to obtain first-hand experience with dose intensive regimens and become familiar with their safe administration.

Mr. Hoyer. On a related matter, I am interested in whether you believe that physicians have sufficient tools at their disposal to relieve the pain associated with disease?

Dr. Broder. The effective alleviation of cancer-associated pain has received an increased amount of attention over the past few years. New methods of pain control have been developed which utilize electrical stimulation, chemical blockade of the pain fibers, or surgical interruption of the pain pathways. These approaches have proven to be effective additions to classical pharmacologic approaches to this problem. Oncologists have become more familiar with ways in which the analgesic effect of narcotics can be significantly enhanced, either by the co-administration of anti-inflammatory agents or antidepressant drugs, or through the administration of the analgesic in a unique fashion, such as directly into the epidural space or the region causing the pain. It is widely felt that physicians currently have adequate resources to control the vast majority of cancer pain situations, but may lack adequate expertise in their optimal utilization. For this reason, many cancer centers throughout the country have developed a multidisciplinary "pain team" specializing in the multidimensional analysis and control of cancer pain.

Mr. Hoyer. Are you aware of any research on whether physicians are reluctant to administer drugs to patients to alleviate pain for fear of engendering an addiction?

Dr. Broder. Because of a better understanding of measures available for the effective control of cancer pain, physicians are less reliant upon narcotic analgesics as the sole agents for use in these situations and, as a result, are less reluctant to prescribe them as part of a coordinated approach to pain management. Research has shown that the most effective control of cancer pain incorporates an active role for the patient in adjusting the dose and/or rate of analgesic administration. Rather than leading to narcotic abuse or addiction, clinical studies have shown such approaches to be among the most successful in controlling cancer pain and optimizing functional status of cancer patients.

ADA BILL

Mr. Hoyer. As you may know, with Congressman Coelho's resignation, I have been sheparding the ADA bill through the House, and I am very interested in the 43 million Americans who have disabilities.

I know that NCI has worked with organizations that serve cancer survivors, and I wondered what you could tell us about how they are faring in our society once they have overcome the challenge of a life-threatening disease like cancer?

Dr. Broder. According to the American Cancer Society (1989), there are over five million Americans alive today who have a history of cancer. Three million of them are five or more years past diagnosis.

The Office of Cancer Communications of the National Cancer Institute has conducted focus groups in which cancer survivors have expressed concern for themselves, families, friends and co-workers. Examples of issues discussed were physical disabilities which affect lifestyle and interpersonal relations as well as employability, insurability and fear of recurrence. Research on the survival issues lag behind the medical advances already made. There is little systematic research which documents the extent of the problems identified by survivors or the best interventions to prevent or alleviate them. NCI is encouraging investigators to propose research which will better document the extent of the problems faced by cancer survivors and design intervention strategies to address these issues.

Of note is one study which is focusing on the insurance and employment issues faced by the survivors of childhood cancer. When completed, this study will provide valuable information on the extent and nature of these problems as well as examine the usefulness of strategies to resolve the issues. Within NCI's Clinical Cooperative Groups, ongoing studies are evaluating the physiologic late effects of therapy for childhood cancer. Another clinical trial, is evaluating an intervention designed to facilitate the return to work of newly diagnosed breast cancer patients. This group also is studying an intervention designed to increase school attendance among children actively receiving treatment for cancer. Such early intervention strategies may ameliorate long-term problems among survivors.

INSTITUTE PRIORITIES

Mr. Hoyer. A variety of studies have specifically linked dietary fat to the high rates of cancers of the breast, colon, rectum, ovary, and uterus, and to the high rate of coronary heart disease among women in America and Western Europe. Yet there have been few attempts to test the prevention hypothesis.

In 1989, 43,000 women died of breast cancer. Every year an estimated 142,000 cases of breast cancer are reported -- of which half of these women will die of the disease. Cancers of the breast, colon, ovary, and uterus occur about four times more frequently among women in the U.S. compared to women in Japan.

Dr. Broder, realizing that the NCI is under constant pressure to fund a great number of grants, and is only able to fund approximately one in every four, it is very important to plan for high priority areas of research. Wouldn't you agree?

Dr. Broder. I would agree, sir. NCI uses its Executive Committee, a body comprised of Institute division directors, the chief executive officer, and myself, as well as a number of chartered advisory bodies, to identify the most important priorities in cancer research. Among these chartered advisory bodies is the National Cancer Advisory Board whose members are appointed by the President. If possible, funding is then made available.

DIET INTERVENTION

Mr. Hoyer. Is it true that of highest priority with the National Cancer Institutes Cancer Prevention and Control Program is diet intervention? If funds were available, would the NCI fund a major diet intervention study?

Dr. Broder. Cancer prevention, and in particular, research on diet and cancer prevention is a high priority for NCI's Cancer Prevention and Control Program. As you point out, diet has been linked to cancer, with scientists estimating that diet may account for 35 percent or more of cancer mortality. And it is true that diet is strongly linked to the high rates of coronary heart disease.

The definitive test of the impact of diet on cancer will likely depend on a large-scale dietary intervention study. The epidemiological and laboratory studies to date provide strong circumstantial evidence, but do not necessarily provide the causal data necessary to prove the role of diet.

While it is true that dietary intervention is of high priority, the Cancer Prevention and Control Program must maintain its ongoing program in smoking, tobacco and cancer. The large-scale community-based study of smoking cessation now underway (COMMIT) is designed to test the effectiveness of using the full resources of communities to combat smoking, and will be the prelude to the American Stop Smoking Intervention Study -- known as ASSIST -- which will disseminate and evaluate the COMMIT results in a base of over 50,000,000 Americans. With smoking responsible for 30 percent of cancer deaths, it is essential that these efforts continue.

Also of high priority for the Cancer Prevention and Control Program are efforts aimed at reducing the grossly disproportionate cancer burden among the Black population, the Native American populations, the elderly, and the poor. These programs also rank at the highest priority level, and reductions in the present resources would cause severe damage to these efforts. Within its available funds the NCI works to maximize the benefits to be derived from its research and application programs.

DIET FIT

Mr. Hoyer. It is my understanding that a project/grant for a large scale, long-term dietary intervention study has been successfully reviewed and recommended for funding, yet, the appropriate plans were not made in the FY 1990 budget and subsequent FY 1991 budget cycle to fully fund the trial -- lest it is sitting around waiting for funding. Are you aware of this project.

Dr. Broder. Sir, I am very aware of this project. The NCI has received an investigator-initiated proposal for a large-scale long-term dietary intervention study. The study, termed DIET FIT by the investigators, was approved with a priority score close to, but outside of, the funding range. The application was designated as an R01 grant and was given a dual assignment to the National Cancer Institute (NCI) and the National Heart, Lung and Blood Institute (NHLBI). The investigators requested support for a prospective prevention clinical trial to determine if a reduction in dietary fat would lower the incidence of breast, colon, endometrial and ovarian cancers, as well as coronary heart disease, in postmenopausal women. The trial would continue for at least 10 years at a total cost of close to $140 million.

Following peer review, the National Cancer Advisory Board (NCAB) reviewed the proposal and agreed that this prospective trial could add to the body of existing knowledge about the potential benefits of low-fat diets. However, in the face of disagreements about the scientific practicalities, and the many scientific opportunities in cancer research, the NCAB did not deem it appropriate to fund a trial of this magnitude as an R01 grant from the traditional research project pool, and voted not to concur with the recommendation of the Initial Review Group regarding this application. The NCAB action was not taken completely on scientific or technical merit per se; rather, it was in accordance with the NCAB's authority to ensure appropriate use of grant, cooperative agreement and contract funds in NCI's support and conduct of research; to assist NCI in identifying priorities for resource allocation; and in enhancing program management and effectiveness. Some NCAB members did not feel that the total cost of $140 million could be justified against competing priorities. Having said this, it is fair to add that some NCAB members did raise scientific and technical concerns about the trial.

The NCI and National Heart, Lung, and Blood Institute (NHLBI) believe that dietary intervention trials are essential to assess the relationship between dietary patterns and human health. Also, dietary intervention trials are an essential component of an overall research program in the areas of prevention and control of specific cancers and coronary heart disease, and in evaluating the potential public health impact of specific dietary modifications.

The NCI and NHLBI are currently planning a workshop to address policy issues, resource needs and directions for cost-effective long-term trials aimed at assessing the impact of dietary change on women's health. Participants will be scientific experts and leaders in the disciplines related to disease prevention, experimental design and public health policy. We anticipate that any recommendations would be further reviewed by the appropriate advisory boards and councils of both Institutes, and funding for any large-scale trial would be contingent on the availability of funds and competing priorities. It is difficult for the NCI to underwrite the DIET-FIT trial within available funds, particularly given the significant outyear costs.

Mr. Hoyer. Dr. Broder, every day we read about what we should and shouldn't eat - the experts change their minds as often as we go to the supermarket. Do you believe that diet-intervention data is needed to help offset such devastating diseases as breast cancer, cancer of the colon, rectum, ovary and uterus, as well as coronary heart disease?

Dr. Broder. Yes, I agree with you that the public has a difficult time assessing what and how much to eat. Unfortunately, the existing studies are largely either epidemiological and compare cancer experiences across different cultures, or laboratory based and give very strong evidence of the role of particular aspects of the diet on cancer. Together the mass of evidence is strongly in favor of a critical causal role for diet in cancer -- so strong that NCI, the Surgeon General, and the National Research Council have developed public guidance regarding overall levels of dietary fat and fiber. We are missing, however, the definitive intervention studies that would provide the information necessary to fully understand the role of diet in cancer and thereby to develop guidelines in which the public will have greater confidence, on which scientists will have greater consensus, and will therefore be adopted by the food system -- the growers, processors, and distributors. Nevertheless, there are enough facts and informed opinions for the NCI to give some guidance to the public and professional community.

Over the past decade, NCI has been working to enable the public to achieve prudent levels of fat and fiber in the diet. In 1985 we set National Goals for fat and fiber levels for the American public. Since that time, we have worked actively with state and local health agencies to enable them to develop nutrition education programs to achieve these goals. The NCI also stresses the positive role of fresh fruits and vegetables, and lowering of salt intake.

Mr. Hoyer. Could the FY 1991 President's Budget Request sustain a major study which would, lets say, cost approximately $7 million per year for the next 10 years?

Dr. Broder. The NCI would not be able to fund such a study for $7 million. We estimate the study would cost minimally $14 million per year. In any case, allocating $14 million of the Cancer Prevention and Control budget line, under the FY 1991 President's budget would result in a severe reduction in funds currently allocated to support minority-focused activities and smoking prevention/cessation initiatives. Within available funds, we would give a higher priority to supporting existing prevention and control activities, plus restoring downward negotiations in grants.

Mr. Hoyer. In your professional judgement, what kind of increase would the NCI need in order to fund such a useful study?

Dr. Broder. The NCI has estimated that the cost of a diet intervention study related to fat and breast cancer would cost approximately $14 million per year for a period of 10 years, that is, a total cost of about $140 million.

BREAST CANCER

Mr. Pursell. About nine percent of all women in the United States will develop breast cancer in their lifetimes. While researchers have made significant advances in breast cancer treatment, breast cancer death rates have not been reduced during this time, because the rate of breast cancer in women has increased in recent decades. This is particularly true among post-menopausal women.

To what do you attribute this increase in breast cancer rates?

Dr. Broder. Data on trends in breast cancer incidence (Second and Third National Cancer Surveys, NCI's Surveillance, Epidemiology and End Result (SEER) Program, Connecticut Tumor Registry) suggest both an overall long-term increase since at least 1940, as well as a more dramatic increase since the early 1980s. Similar patterns in breast cancer incidence have been observed in other Western countries, including all five Nordic countries.

A number of factors have been posed which could explain the increase in breast cancer incidence. Epidemiologic studies have supported an association between reproductive factors and breast cancer, although the evidence is occasionally conflicting. Published reports have implicated the trend toward delayed childbearing and the increased use of oral contraceptives. Most scientists agree that delaying the age at which a women has her first full-term delivery (to past 30) is a risk factor. Therefore, societal changes probably contribute in part to this problem. However, a report published in 1989 based on the Connecticut historical data has suggested that changes in reproductive patterns which occurred earlier in the 20th century do not completely explain the trends observed for postmenopausal breast cancer patients. More recently, other researchers have concluded that their analysis of data for a cohort of women in a large pre-paid health plan documents changes in the prevalence of a known biological risk factor (receptor status) for breast cancer. These researchers interpret these facts as implicating hormonal factors in the rising incidence. Female hormonal supplementation is an issue under study.

Other possible explanations include changes in age at menarche (first menstrual period), age at menopause, surgical removal of ovaries, multiparity, lactation, and body weight. None of these factors completely explain the overall trends in breast cancer in the U.S. or in other Western countries with similar incidence trends.

Analysis of long-term trend data for breast cancer incidence coupled with SEER data reveal that the rates show an increasing trend from approximately 1940 through 1982. The sharp rise in incidence since the early 1980s is largely due to in situ and localized disease, particularly among women over the age of 50, which constitutes the vast majority of breast cancer cases. Most likely this apparent rise represents in part better screening. Data on tumor size from the SEER Program show a shift in the tumor size distribution towards smaller tumors for cancers that are classified as localized. These findings suggest that one possible explanation for the trends is a change in breast cancer screening rates, since breast cancer screening would tend to detect more disease at all stages, but this would be accentuated in disease at earlier stages. Although national data indicate low utilization of breast cancer screening by women in the U.S., the recent explosive growth in the sale and installation of new low dose equipment for mammography portend increasing utilization of screening mammograms. Current evidence supports the hypothesis that early detection is the major determinant for the recent increase in breast cancer incidence in women over the age of 50. The evidence for what is happening in women under the age of 50 is not so clear. Changing reproductive risk factors in the population appear to have played a lesser role in the breast cancer increase. The role of other lifestyle factors, such as dietary practices, continues to be under investigation. The NCI views these problems very seriously. Virtually every program in the Institute is participating in efforts to solve these problems.

Mr. Pursell. Frequent examinations and early detection are critical to increasing the survival rate. Are women of all ages, and particularly post-menopausal women, more likely to be tested today?

Dr. Broder. Data from several surveys suggest that breast cancer screening, i.e., using mammography, is rising among women of all ages in the United States. According to the 1987 National Health Interview Survey, the 1987 Behavioral Risk Factor Surveillance System, and the 1987 American Cancer Society (ACS) Gallup Survey, mammography rates have increased rapidly over the last four years. In the 1983 American Cancer Society Gallup Survey, 13 percent of women 40 years and older reported they have yearly mammograms. By 1987, this rate doubled to 26 percent in the 1987 Behavioral Risk Factor data for women over 50 years of age, and to 23 percent in the 1987 Health Interview Survey.

On the contrary, other forms of breast cancer screening are stable. Clinical breast examination (CBE) and breast self-examination (BSE) have not increased significantly over the last four years. In 1983, 50 percent of women of all ages reported they had yearly clinical breast exams. Very little change in CBE was observed for all women by the 1987 ACS Gallup Survey and for women 40 years and older by the 1987 National Health Interview Survey for women. Likewise, monthly breast self-examination declined slightly from the 1983 ACS Survey (27 percent) to the 1987 ACS Survey (23 percent). The NCI is exploring ways of encouraging better mammography utilization by developing culturally-relevant approaches to the various population groups in the Nation.

Of the three types of breast cancer screening cited, mammography and clinical breast examination have been shown to reduce mortality from breast cancer by approximately 30 percent. Thus, although considerable progress has been made to increase mammography rates in women, current utilization of mammography and clinical breast examination are far lower than the NCI goals set forth in its year 2000 cancer control objectives for the nation, i.e., that at least 80 percent of women aged 50-70 will have received a clinical breast exam coupled with a mammogram within the preceding year. The NCI feels that annual mammograms and breast exams could make a major impact in women over 50. This is a major focus of the Institute.

Mr. Pursell. Are we doing enough to encourage women to be tested?

Dr. Broder. Much needs to be accomplished in order to educate and encourage older, minority, low-income, uninsured, and underinsured women to receive mammographies. NCI's Special Populations Studies Branch and Cancer Control Applications Branch are funding a variety of grants to improve the use of mammography, and to test outreach methods within hard-to-reach populations. Grantees are working with community groups, health care providers and public health agencies as part of this effort. The NCI sponsored an important Mammography Women's Leadership Summit involving women from the Executive Branch and the Congress as well as private sector to mobilize better communication.

A priority program of NCI's Office of Cancer Communications (OCC) is its Breast Cancer Screening Education Initiative. OCC is working through the media, the Cancer Information Service, organizations with large numbers of women, and physician organizations to increase mammography and clinical breast exam use. Special efforts for minorities are being developed through OCC's Minority Education program. By addressing the system from both ends -- consumers and health providers -- OCC hopes to increase women's requests for mammograms, as well as increase physicians' referral rates. The program requires extensive development of intermediary and physician group contacts, and needs assessments along with media planning and follow-up. The kickoff occurred in September 1989, and activities will continue at least through 1991. With continued support within NCI and cooperation from other organizations, these efforts should elicit increased use of mammography, with expected long-term reduction in the breast cancer death rate.

Mr. Pursell. Does your Institute coordinate with CDC and others to identify women whose family have a history of breast cancer, to encourage them to undergo frequent examinations?

Dr. Broder. Our Division of Cancer Prevention and Control and the Center for Chronic Disease Prevention and Health Promotion of the Centers for Disease Control are undertaking a joint planning effort with other Federal agencies to identify additional actions which need to be taken to increase the early detection of breast cancer. Included in this joint effort is the issue of encouraging women with a known history of familial breast cancer to undergo frequent examinations, thereby increasing the likelihood of detecting breast cancer at an earlier stage, when it is more easily treatable.

DIET AND CANCER

Mr. Pursell. Certain cancer rates, including breast cancer, are much higher in American women than in Japanese women, and experts agree that this may be the result of diets. What studies has the Institute sponsored to study the effect of diet on these cancer rates?

Dr. Broder. Evidence continues to accumulate from epidemiologic and experimental studies that dietary and nutritional factors may contribute to a significant portion of cancer in humans. Evidence for their role comes from large international variations of cancer incidence, and from studies of migrants, whose cancer rates approach those of the host country during the process of acculturation. NCI has conducted a number of investigations designed to identify and evaluate specific dietary constituents that may be involved as cancer risk factors. A feasibility study was conducted to test whether a low-fat diet (20 percent of calories from fat) compared with the usual American diet (approximately 40 percent of calories from fat) would reduce breast cancer incidence in 45- to 69-year-old women. The feasibility study indicated that women can be recruited to join a large-scale, long-term prevention trial and will agree to accept a randomization assignment. It was also shown that women will adopt and maintain a low-fat eating pattern for a period of at least two years. Considering the results of this feasibility study, it is likely that a large scale dietary intervention study will be successful and that it is desirable to conduct one.

The NCI is currently supporting a multi-institutional study to demonstrate the feasibility of a low-fat dietary intervention in Stage II post-menopausal breast cancer patients receiving tamoxifen. Low-fat dietary therapy, if effective in prolonging survival and reducing recurrence rates, may be an alternative to treatment with toxic drugs or could be considered as an adjuvant to other therapy. However, a consensus does not exist here.

Breast cancer mortality rates among women in China and Japan are about one-fifth those of white American women. Among successive generations of Asian women who have migrated to the United States, however, breast cancer rates have increased to approach those prevailing among Caucasians. The rising trend is suspected to be related to gradual adoption of the Western diet, which is high in fats and calories. This hypothesis is being tested in a population-based case-control study of breast cancer among American women of Asian ancestry, living in Los Angeles, San Francisco, and Hawaii. In this study, coordinated by NCI, detailed dietary histories have been collected to assess the role of nutritional risk factors, especially in childhood and adolescence. In addition, serum levels of lipoproteins, fatty acids, micronutrients, and endogenous hormones will be measured to evaluate their relationships to breast cancer risk. In a separate investigation being coordinated by the NCI, a large-scale, case-control study of breast cancer in the general U.S. population will assess a number of possible risk factors, including the role of adolescent dietary patterns and alcohol consumption. Furthermore, in a study at the University of California at San Francisco, the risk of breast cancer will be investigated in relation to constituents of breast fluid secretions and to dietary factors among Chinese-American woman.

Investigations into the patterns of cancer among Asian-Americans are being complemented by studies conducted in their ancestral countries. For example, stomach cancer afflicts Japanese- and Chinese-Americans much more often than Caucasian-Americans. In a high-risk area of China, stomach cancer patients were found to consume more salted foods and local sour pancakes, and less fresh vegetables than controls. Protective effects were noted especially for vegetables of the allium class, including garlic and onions. To evaluate the role of diet on precancerous lesions of the stomach (i.e., chronic atrophic gastritis, intestinal-type metaplasia, and dysplasia), subjects in the high-risk area of China are being enrolled in a screening program to detect early cancers and to compare questionnaire responses with biochemical marker data. In another investigation, scientists at Stanford University are coordinating a collaborative case-control study of colon cancer among Chinese in both China and the United States, with emphasis on the role of dietary habits.

Esophageal cancer also occurs more often among Chinese-Americans than Caucasian-Americans. Dietary factors will be evaluated in Linxian, China, which has the world's highest rates of this cancer. A large-scale, five-year randomized intervention trial continues to evaluate whether certain groups of vitamins and minerals can inhibit late-stage progression to cancer in a high-risk population with multiple micronutrient deficiencies. One component of the trial focuses on persons with esophageal dysplasia and another on villagers from the general high-risk population.

Because of the strong relationship between obesity and endometrial cancer, a multicenter case-control study of this cancer is focusing on dietary components as possible risk factors. The dietary interview is designed to measure intake of all major nutrients, with a special emphasis on fat and calories. Anthropometric measurements will be used to evaluate the role of fat distribution patterns and physical activity at various ages. Hormone assays will be carried out on blood samples to assess the relationship of obesity, diet, endogenous hormones, and cancer risk. Fatty acid profiles of plasma, red blood cells, cheek cells, abdomen and arm aspirates, and surgical abdominal fat will also be determined on a sample of the subjects.

A recent NCI study found that colo-rectal cancer cases were more likely than controls to have stool mutagenicity. This finding is intriguing, since heterocyclic arylamines are formed from the pyrolysis (cooking) of amino acids when red meats are cooked at high temperatures by broiling, baking or frying. Although their biological effects in humans are unknown, a number of these substances are mutagenic in the Ames test (Salmonella TA98) and carcinogenic in laboratory animals, producing tumors of the liver, small intestine, and colon. Using a case-control approach, the relationship between mutagens produced during cooking and the risk of colo-rectal cancer is being investigated. Patients with newly-diagnosed colo-rectal cancer are being compared to controls with regard to usual diet, immediate past diet, cooking practices, and fecal mutagenicity.

INTERNATIONAL COLLABORATION

Mr. Porter. Dr. Broder, I recently met with a group of international researchers in the areas of cancer and AIDS. There was a broad consensus that more progress could be made if a greater degree of international collaboration, especially through education and training, was supported by research centers around the world. Do you agree, and if so what priority areas should be addressed through international collaboration?

Dr. Broder. Yes, we do agree in general. The need for international collaboration on AIDS has never been more important. AIDS has clearly been shown to be a disease which knows no national boundaries, having now been reported from over 140 countries. International studies have already contributed critical information related to understanding the natural history of AIDS, major modes of HIV transmission and risk factors for HIV infection. NCI also agrees that training and education are essential in our worldwide efforts to control AIDS. NCI's intramural AIDS program trains both clinicians and basic scientists in the biology, pathogenesis and treatment of AIDS. In addition, NCI scientists involved in international collaboration take an active role in training investigators at research centers around the world. Such sharing of information and educating scientists worldwide is critical to future progress against this disease. Studies in other countries have provided vital information in such areas as characterization of existing and identification of new infectious agents, understanding heterosexual transmission and documenting the effects of AIDS upon women and children. Research conducted in other countries is of direct benefit to U.S. citizens and often provides unique opportunities to improve our knowledge and understanding of HIV infection and AIDS.

NCI believes that international collaboration is vital to achieve worldwide progress against the AIDS epidemic. Some of the priority areas NCI has identified for international study and cooperation include epidemiologic and natural history studies of HIV-1 and HIV-2, HTLV-1 infection, and studies characterizing the variability of the human response to HIV infection. Investigations are ongoing in New Guinea, South America (Venezuela), Central America (Columbia), West and Central Africa, and the Caribbean (Jamaica, Trinidad-Tobago). Other priority areas include AIDS vaccine development and AIDS drug development. Some of the specific international projects are briefly described below:

NCI has participated in the establishment of an international registry of AIDS victims which documented dates of HIV seroconversion in order to evaluate cofactors and trends of AIDS risk. Thirty-eight investigators from several countries -- Canada, U.S., Greece, France, U.K., Denmark, Italy, Japan and Australia -- have contributed over 1,115 subjects for analysis. This database will provide valuable information about the natural history of HIV infection in various populations worldwide. The main goals of this project are to obtain data on the natural history and time to AIDS diagnosis of HIV seroconverters and to define cofactors which predict for disease progression including possible genetic factors.

Active collaborations to isolate and characterize known retroviruses from different areas of the world have been initiated. The objective of these efforts is to find out whether strain differences can provide a clue to the clinical variation in progression to AIDS or in "natural resistance", if such exists. Broad-based population surveys are being undertaken in Tanzania, Ghana, Brazil, New Guinea, Barbados and Jamaica to monitor prevalence and trends in HIV infection rates in high risk populations and in the general community. In New Guinea, attempts are being made to obtain cultures on a retrovirus that is thought to be distinct from other strains isolated to date.

Other projects include study of the human lymphotrophic viruses as etiologic agents or co-factors in adult T-cell leukemia (ATL), AIDS, Kaposi's sarcoma, cervical cancer, and lymphoma. In Africa, a multicenter study is ongoing to enhance cancer surveillance in selected African cancer registries and to look for trends in cancer incidence linked to HIV epidemics. Projects aimed at studying the epidemiology and etiology of HIV and HTLV-1 infection and human malignancy are also ongoing in Greece, France, Jamaica and Trinidad. A major focus of this HIV research is the longitudinal follow-up of cohorts at risk for developing AIDS to document modes of transmission, the natural history of progression and the development of malignancies, and the predictors of risk.

Prospective studies of homosexual male cohorts in Denmark, Jamaica and Trinidad are being conducted to determine the natural history, genetic, racial and ethnic factors associated with HIV infection and the prevalence of retroviral coinfections. Heterosexual cohorts are being studied in Greenland, Trinidad and Jamaica to investigate prevalence of HIV infection, natural history and associated risk factors.

NCI sponsors a program which supplies international AIDS investigators with AIDS-related agents needed for work in vaccine development, immunologic testing and for assaying for the presence of retroviral activity. NCI is also funding work in AIDS vaccine development at the National Veterinary Institute of Sweden. Immune stimulating complexes (ISCOMS) which contain HIV envelope components are being developed to enhance the immunizing potential of the viral proteins. This ISCOM technology was developed in Sweden in the feline leukemia virus model system and is now being adopted for use in HIV vaccine development. The ISCOMS appear to be a more effective adjuvant than even Freund's adjuvant and this work appears promising enough to warrant testing in monkeys and other primates.

NCI also has collaborations in drug development with Belgium scientists in the investigation of the molecular pharmacology of specific drugs with anti-HIV activity.

In conclusion, NCI's priority areas for international collaboration include epidemiologic studies of the natural history and modes of transmission of HIV, HTLV-1, and HTLV-2 infection; the natural history of HIV-related malignancies; AIDS vaccine development; and AIDS drug development. Continued international collaboration is essential to the worldwide control of this disease.

Mr. Porter. Has the NCI been involved in any work in the Soviet Union, especially in the wake of the Chernobyl disaster?

Dr. Broder. NCI epidemiologists have been actively engaged with post-Chernobyl activities starting with the International Atomic Energy Agency (IAEA) meeting in Vienna in August, 1986. We also participated in the 1987 IAEA-WHO epidemiology meeting in Vienna sponsored by the USSR. In 1989, we joined a US-USSR research group organized by the Department of Energy and the Nuclear Regulatory Commission, attending an organizational workshop in Kiev in September, 1989. We are spearheading the epidemiologic collaborative efforts being made by this group, and have taken responsibility for organizing initial discussions on thyroid function and disease, leukemia, and a proposed survey of child health.

Invitations are going out for exchanges between Soviet scientists and scientists at NCI. Dates have been set for a US-USSR workshop on thyroid function to be held in Kiev in November. NCI scientists have been contacted regarding advice for medical care and surveillance of individuals exposed to the Chernobyl fallout.

One staff member from NCI's Radiation Effects Branch has been especially involved in work in the Soviet Union in connection with the Chernobyl accident in the following ways:

1) As a consultant to the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), he participated in the preparation of a document titled "Exposures from the Chernobyl accident", which was endorsed by UNSCEAR and published as an Annex to their 1988 report to the United Nations General Assembly.

2) As a member of a working group of the US-USSR Joint Coordinating Committee on Civilian Nuclear Reactor Safety, he participated in September 1989 in the preparation of proposals for joint research in the area of environmental monitoring and modeling.

3) In March 1990, IAEA requested his assistance in responding to a request from the USSR to evaluate the effectiveness of the steps taken to safeguard the health of the population in the area affected by radioactive contamination following the Chernobyl accident in order to enable the population to live safely in these areas.

In addition to the Chernobyl-related work, other scientific exchanges are taking place. Recent changes in the political climate within the Soviet Union and eastern-European nations has evidenced itself in a dramatic widening of communication channels with the West. More collaboration is taking place and expectations are high that this positive trend will continue. The Soviet coordinator for the U.S.-Soviet bilateral program has proposed many more visits of Soviet cancer researchers to American laboratories; furthermore, the Soviet government now permits their scientists to visit U.S. laboratories for longer periods of time.

The All-Union Cancer Research Center (AUCRC) in Moscow is conducting clinical trials in parallel to some being conducted here. A treatment protocol using cisplatinum in testicular cancer is now nearly at full patient accrual and three additional protocols dealing with colon and breast cancer were started last year. Working in collaboration with these studies, an NCI investigator has just returned from a two-month visit to Moscow. An American delegation of prominent cancer researchers will be visiting Moscow this March to assess the progress of these treatment studies. The Soviet Union has traditionally exhibited strong excellence in mathematics and physics research. We are exploring appropriate cancer-related collaborations in such areas of excellence.

Preliminary discussions are underway exploring the feasibility of establishing two U.S.-Soviet cancer institutions, one in Moscow and one in the Soviet Far East. The NCI is prepared to assist the Soviets in the training of their future scientific and clinical faculty. Long-term training of Soviet scientists in the West will acquaint them with newer techniques which should translate into more use of state-of-the-art treatment regimens and foster further collaboration.

NCI is preparing to provide eastern European cancer institutions, including those in the USSR, its Physician Data Query (PDQ) and CANCERLIT databases using compact disc technology. The data-bases provide the latest information in both basic and clinical cancer research. NCI envisions a cooperative demonstration and evaluation project at a selected number of East European institutions, including the AUCRC in Moscow. In addition, Soviet researchers have expressed interest in products manufactured by U.S. biotechnology and pharmaceutical industries, and in the American publications related to cancer research, treatment, and prevention. Unfortunately, some NCI programs can be approved by political forces that are unpredictable and out of our control.

CANCER STATISTICS

Mr. Porter. Dr. Broder, this committee has discussed with you in the past, the major discrepancy in cancer mortality rates for Blacks and whites. What progress has been made in the past year on closing this gap?

Dr. Broder. For 1987, the most recent period for which data is available, the age-adjusted cancer mortality rate for Black Americans is approximately 30 percent higher than the rate for whites (218.2 per 100,000 for blacks versus 168.0 per 100,000 for whites), whereas the corresponding cancer incidence rate is similar for both races. For 16 of the most common anatomical sites of cancer, the age-adjusted cancer mortality rate for Blacks exceeds that for whites for all but five of the major sites, is less than that for whites in four sites, and is similar for one site.

Available data for 1987 indicate that for all cancer sites combined, when compared to whites, Blacks have a similar risk of developing cancer and a five-year survival rate which is 30 percent lower than expected. High incidence rates coupled with low survival rates lead to a mortality rate 30 percent higher than that for whites, 40 percent higher for black males and 20 percent higher for black females.

Recognizing the critical need to give special attention to the disproportionate burden of cancer borne by Black Americans and the important task of delivering health promotion messages to counter the practice of targeting this community for activities which promote the use of products that are known to have serious health consequences, the National Cancer Advisory Board (NCAB) instituted the National Black Leadership Initiative on Cancer (NBLIC). Dr. Louis Sullivan, until his appointment as Secretary, DHHS, was a member of the Board, and chaired the NBLIC, whose creation he stimulated. Dr. Sullivan deserves great credit for having set the stage for better prevention, diagnosis, and treatment of cancer in the Black community. Dr. Sullivan recognized that to really make a change, a program had to be created and integrated within the community. This is in fact the intent of the NBLIC.

Fundamental to this initiative is the mobilization of individuals who are committed to achieving a high level of cancer prevention awareness among Black Americans. The message at the heart of this effort is that cancer is, to a great extent, preventable. Prevention and control of cancer in minorities will depend critically on achieving marked changes in avoidance of tobacco products, adoption of high-fiber, low-fat diets, involvement in screening and early detection activities, and gaining access to state-of-the-art care and treatment.

As a first step in mobilizing a significant part of the minority community in this effort, NCI recruited and supports a regional coordinator in each of the six cities that served as the location for the regional meetings of the NBLIC. These meetings, which took place over the course of the past year in Atlanta, Los Angeles, Chicago, New York, Washington, D.C. and Houston, brought together Black leaders from many fields -- academia, clergy, medicine, business, public health, the media, state and local legislatures -- to develop strategies for initiating or enhancing cancer control and prevention activities in the Black communities of their respective regions. The regional coordinators represent an NCI presence in these communities and will serve a liaison role in identifying community resources, facilitating their most effective utilization, assisting communities in obtaining and optimizing support from NCI in implementing local cancer prevention and intervention programs.

An additional part of the NCI community-based plan is to provide grant-supported cancer prevention and clinical research in underserved populations. An essential criterion for these awards is that the grantee institution have demonstrated the ability to work in collaboration with the minority community in programs of education and health promotion. Reduction in mortality among minority populations at high risk for specific cancers should be possible if improved access to effective therapeutic interventions can be assured. The diagnosis of cancer at an earlier, more treatable stage can be expected to accompany an increase in screening programs that are conducted in high density minority population areas. It is anticipated that up to three such awards will be made during FY 1991.

NCI currently is conducting trials on smoking prevention and cessation which address the special needs of the Black community. NCI will continue to work with a network of Black leaders to disseminate the most effective smoking prevention and cessation strategies as results of these trials become available.

A special effort which is complementary to the planned expansion of the Community Clinical Oncology Program and will serve predominantly minority communities is in the process of award. The program will enhance current NCI efforts designed to close the gap in survival between white and Black cancer patients by enabling academic and community oncologists with large minority populations to gain enhanced access to state-of-the-art cancer management through participation in treatment and cancer control clinical trials.

NCI has an ongoing program designed to determine how to increase the use of Pap smears and followup medical treatment for low income and Black women with early stage cervical cancer. NCI also plans to continue and expand a number of programs designed to enhance the capacity of state and local public health departments to administer cancer screening programs to low income women.

An expansion of the Surveillance, Epidemiology and End Results (SEER) Program is also undergoing review in order to provide more adequate statistical coverage of minority populations.

TROPICAL PLANT COLLECTION/DRUG DEVELOPMENT

Mr. Porter. Your budget justification indicates that NCI places a high priority on plant collection in Africa, Central and South America, and South East Asia.

I understand the screening process is only testing the plants for anti-cancer and anti-AIDS potential. Does the NCI have plans to expand the testing, or have they already done so?

Dr. Broder. The comparatively small scale of the present collections (300 grams to one kilogram of dried plant material per sample) is generally only sufficient to provide the extract for anticancer and anti-HIV testing and initial fractionation studies of active extracts. In addition, the long term aim of NCI is to maintain its repository of extracts for testing in new antitumor and anti-HIV screens as they develop. Expansion of testing beyond such limits would require a considerable increase in resources to support expanded collections, extra storage and processing facilities. Nevertheless, NCI will cooperate with any sister agency in government to pursue relevant leads whenever possible.

Mr. Porter. Are the collected plants being kept alive in the United States?

Dr. Broder. Plants are not being kept alive in the United States, nor are seeds being routinely collected. The export of live plant material from the collection countries would certainly raise the suspicions of authorities in those countries and might represent a source of misunderstanding with local authorities. In addition, importation of live plant material (as opposed to dried material) into the United States is not routinely permitted by U.S. authorities.

Mr. Porter. Are you keeping seeds?

Dr. Broder. The preservation of seeds in a viable state is a difficult and costly operation which would greatly complicate the collection program. In the event of isolation of a promising drug from a plant, NCI would want to collaborate with the country of origin in promoting the cultivation of the plant so as to provide maximum benefit to that country. We particularly want to convey a sense of respect for local culture and reverence for the local ecology. We will cooperate with local officials in regard to seed collection and preservation.

Mr. Porter. Due to the unprecedented nature and size of the plant collection that will result, are there any plans to open access to the plants to private interests?

Dr. Broder. The scope of the NCI plant collection is certainly unprecedented in terms of number samples, but the small size of the individual sample (300 grams to one kilogram of dried weight per sample) does not permit the widespread distribution of extracts to private interests. The size of the samples is generally only sufficient to permit anticancer and anti-HIV screening, and preliminary fractionation of active extracts. In addition, a long term aim of NCI is to maintain repository of extracts for testing in new antitumor and anti-HIV screens as they are developed. Uncontrolled distribution of this valuable resource might rapidly empty the repository, and defeat the objectives of the NCI drug discovery program.

Two years after receiving and processing of the plant material, NCI could consider requests for samples from their repository based strictly on the scientific merit and the relevance of each request to the primary mission of NCI, namely the treatment of cancer and AIDS. Tight control in considering such requests would be exercised by an NCI committee in view of the limited size and availability of the present samples. NCI would require close involvement in the discovery and development processes of any new drugs, probably under terms of the Cooperative Research and Development Agreement.

Mr. Porter. Shouldn't we ensure that, if any profits result eventually from this plant collection activity, the country of origin shares in the profits?

Dr. Broder. NCI is presently formulating a policy whereby the country of origin of a plant (or other organism) yielding a new drug will receive both short-term benefits and long-term compensation in the form of a share of the royalties resulting from drug sales. Final arrangements would depend on advice and input from the Office of the General Counsel.

Mr. Porter. Do you have in place, or do you have under consideration a mechanism to ensure such international profit sharing?

Dr. Broder. In the short term, scientists from collection countries will be invited to visit NCI to discuss the drug discovery program and, if space and resources permit, participate in the drug discovery and/or development process. This policy is, in fact, already operative. In licensing a Government-patented drug to a pharmaceutical company, NCI will negotiate with the company for inclusion of terms in the licensing agreement requiring payment of a percentage of royalties accruing from sales of the drug, to the country of origin. In addition, when approving licensees, NCI will consider the willingness of the applicant to seek as its first source of supply the country from which the plant originated.

NCI - AIDS: AZT AND ddI

Mr. Porter. On page 77 of your budget justification you state that ddI will shortly be compared to AZT in a large study designed to examine its efficacy and long term toxicity. When will this study begin? When do you expect this study to be completed?

Dr. Broder. Two large studies comparing AZT and ddI began in October of 1989. One study compares AZT with two doses of ddI (500 and 750 mg/day) in AIDS and ARC patients who had either never received AZT or had received AZT for less than one year. A second study compares AZT with the same two doses of ddI in AIDS and ARC patients who have received AZT for over one year and are likely to have developed resistance to AZT. A third study, comparing three doses of ddI in patients who cannot tolerate AZT began at the same time. Developed at NCI, ddI was licensed to Bristol-Myers under the Federal Technology Transfer Act.

Completion of the studies will depend in part on how fast patients enroll in the studies. Data from one or more of these studies may be available as early as the end of 1991. The studies are reviewed about every six to nine months; if there are striking results, the data will be made available before that time. These studies are under the jurisdiction of the NIAID.

Mr. Porter. Assuming favorable results from further testing, when will ddI be available to the general AIDS population?

Dr. Broder. As a result of the Phase I study conducted by the NCI and preliminary results from other Phase I studies of ddI conducted by the NIAID and Bristol-Myers-Squibb Company, ddI was made available in October of 1989 to patients who could not tolerate AZT or who were progressing on AZT by the regulatory mechanisms of a Treatment IND and Open Label Protocol. The availability of ddI as a prescription drug will depend on the completion and results of the large comparison studies. While ddI is under study, it is not possible to draw conclusions about final safety and efficacy.

Mr. Porter. What do you currently know about the toxicity of ddI as compared to that of AZT? Expand on the explanation in the budget justification.

Dr. Broder. The toxicities of ddI are quite different from those of AZT. The most common toxicity in patients taking AZT is bone marrow suppression, resulting in anemia, low white blood counts (leading to infection), and low platelet counts (leading to bleeding). Some patients also develop muscle wasting, nausea or vomiting. Patients have died from AZT-induced seizures. The most troublesome toxicities in patients taking ddI are peripheral neuropathy (causing pain in the feet) and, in a small percentage of patients, pancreatitis. Rare patients have died of pancreatitis while taking ddI, and studies are underway to determine the role of the ddI, versus other drugs, alcohol, or the underlying disease, in these deaths. One of the aims of the large comparative studies will be to gather information on the relative safety and efficacy of AZT versus ddI.

It is true that some AIDS patients taking AZT for more than one year begin to have declines. It is possible that this is in part because the AIDS virus develops resistance to AZT in many patients at about that time. Other drugs, such as ddI, may still benefit such patients. AIDS is a very variable disease, and a given patient who does not opt to take AZT may certainly live longer than another given patient who is taking AZT. However, patients taking AZT generally live longer than similar patients not taking AZT. For example, in a San Francisco study of aerosolized pentamidine in AIDS patients who had had Pneumocystis carinii pneumonia (all patients were taking aerosolized pentamidine) 85 percent of patients who took AZT were alive at nine months, while only 47 percent of patients who did not take AZT were alive at that point in time.

Mr. Porter. Some health care providers have told me that they see initial improvements in AIDS patients who receive AZT treatment. However, if the treatment is continued beyond 12 or 18 months, they begin to see great declines. By contrast they report that patients who do not opt to receive AZT treatment often live much longer than the AZT patients.

What is the average survival for an AIDS patient who receives AZT treatment?

Dr. Broder. In the Phase II trial of AZT (which involved patients with severe AIDS-related complex and AIDS patients who had had Pneumocystis carinii pneumonia), the median (average) survival of patients taking AZT was about 22 months. There is a general consensus that, at least for patients with advanced disease, AZT can start losing its protective effects after one or two years. Nevertheless, AZT and other treatment advances have clearly prolonged survival and alleviated suffering due to AIDS. Randomized, placebo controlled trials have demonstrated the efficacy of AZT. The median survival of patients with AIDS was about 40 weeks.

Mr. Porter. How does that compare with the average survival for patients who refuse AZT treatment?

Dr. Broder. In contrast, the median survival of patients randomized to the placebo arm was about nine months. In a separate study conducted in San Francisco of aerosolized pentamidine in AIDS patients who had had Pneumocystis carinii pneumonia (all patients were taking aerosolized pentamidine) 85 percent of patients who took AZT were alive at nine months, while only 47 percent of patients who did not take AZT (generally because they refused therapy) were alive at that time point. Finally, in data collected from the Department of Health of New York State, the 18 month survival of homosexual patients with AIDS increased dramatically from 35 percent in patients diagnosed in 1985 (before the availability of AZT) to over 63 percent in 1987. It is almost certain that the release of AZT during that period contributed to this trend. It is also worth stressing that in some adults and children with AIDs-related dementia, AZT can bring about significant mental improvement, not necessarily reflected in the death-rate statistics.

Mr. Porter. If these statistics are not available, why are they not available?

Dr. Broder. The statistics are available and have been submitted.

Mr. Porter. When will this data be available?

Dr. Broder. The data are currently available.

Mr. Porter. What do we know about the long term effects of AZT?

Dr. Broder. The most common toxicity in patients taking AZT is bone marrow suppression, resulting in anemia, low white blood counts (leading to infection), and low platelet counts (leading to bleeding). This toxicity is most troublesome in patients with advanced AIDS, and becomes more common and more severe with continued usage. In part because of this toxicity, the recommended dose of AZT has been lowered to 600 mg/day. However even with this lowered dosage, almost half of AIDS patients taking AZT will develop substantial bone marrow toxicity during the first year of therapy. Some patients have also been reported to develop muscle wasting (myositis) after a year of more of AZT use. At the present time, no patient has received AZT for much more than four years, so we don't have data beyond that point. AZT is an important first step, but it is still only a first step.

Mr. Porter. At what point do the toxic effects of AZT outweigh its benefit?

Dr. Broder. We know from the Phase II study of AZT that the survival of AIDS patients taking AZT was dramatically improved over those taking placebo over a six-month period of time.

However, we do not know at what point the toxicity of AZT may outweigh its benefits. This is largely because once AZT was found to prolong survival in patients with AIDS, it was felt to be unethical to conduct a placebo-controlled study in this same population. In addition, it was quite doubtful that enough patients would enroll in such a study to yield meaningful results. There is presently, however, a study comparing AZT with ddI in patients who have had prolonged treatment with AZT, and such a study should help answer the question of the optimum treatment for this population.

Mr. Porter. If we don't have good data on the long term benefits, when will we have this information?

Dr. Broder. In regard to earlier stages of HIV infection, two studies have recently shown that HIV-infected patients with 500 or less T4 cells/mm^3 and few or no symptoms who take AZT have less short-term disease progression than those who receive placebo. A Veterans Administration cooperative study now underway is addressing the question of whether it is preferable to start AZT early in such patients or to wait until the T4 cells have dropped below 200 cells/mm^3.

HEMOPHILIA

Mr. Porter. I understand that the hemophiliac population in the U.S. is virtually 100 percent HIV positive. Is this accurate?

Dr. Broder. Research has shown that the prevalence of human immunodeficiency virus (HIV) in the U.S. hemophilia population is approximately 55 percent. Among those with severe classical (type A) hemophilia, the prevalence is about 75 percent, while it is nearly 95 percent in the subgroup that was intensively treated with HIV-contaminated plasma products. This rate is decreasing because hemophiliacs are now, and have been for some time, receiving blood products which have been screened for HIV through the test that derived, in part, from NCI's blood screening technology.

Mr. Porter. Can hemophiliacs benefit from AZT treatment? Can they benefit from ddI treatment?

Dr. Broder. Hemophiliacs have been included in several trials of AZT. While no study has formally shown that AZT prolongs survival in this population, the experience indicates that it has anti-HIV activity in hemophiliacs. (The NIAID-supported AIDS clinical trials group [ACTG] looked at the toxicity of AZT in hemophiliacs and found that it was reasonably well tolerated in this population.)

Hemophiliacs have received ddI in an NCI Phase I trial and in other trials. While the experience with ddI is more limited than that with AZT, hemophiliacs do not appear to be different from other patients in their response to it. We do need to learn more about whether hemophiliacs may be more sensitive to ddI toxicity than other patients, either because of their bleeding tendency or their high rate of hepatitis. Data obtained from hemophiliacs who are enrolled in ongoing controlled trials of ddI and from the

(Expanded Access Program) should help resolve these questions. The Expanded Access Program is the FDA's parallel track program whose goal is to increase the number of patients accrued to any AIDS trials. A primary side-effect of the toxicity of AZT is bone marrow suppression; ddI tends to spare the bone marrow, but there is a small rate of acute pancreatitis as a side-effect with ddI. In patients with hemophilia, this side-effect could bring about bleeding in the abdomen. Until more is known, we are not recommending the use of ddI in hemophiliacs except under carefully controlled study conditions.

HEREDITY AND COLON CANCER

Mr. Porter. Briefly, what role does heredity play in the development of colon cancer in an individual?

Dr. Broder. Colon cancer causes over 60,000 deaths in the U.S. each year and is second only to lung cancer as the cause of cancer deaths. Treatment with chemotherapeutic agents and/or radiation has not been entirely successful, so that surgical resection is still the treatment of choice. The lifetime risk for colorectal cancer in the North American population is about five percent.

Based on epidemiological studies, environmental factors play an important role in the pathogenesis of both polyps and colorectal cancers. Further evidence suggests a substantial genetic contribution to the risk of colon cancer. The polyposis syndromes, familial polyposis coli and Gardner syndrome, and the nonpolyposis varieties, cancer family syndrome and site-specific inherited colorectal cancer account for about five percent of all colorectal cancer cases.

There are data to indicate that in addition to the abovementioned genetically defined syndromes, colorectal cancer tends to cluster in families. The first degree relatives of colonic cancer patients appear to have a two- to three-fold risk of developing colon cancer. Patients with an inherited predisposition for developing hundreds of polyps (called familial polyposis) are at nearly 100 percent risk of colon cancer by age 40. However, since this syndrome is quite rare, it contributes only slightly to the overall incidence of colon cancer. This inherited susceptibility, along with well-recognized environmental risk factors, support the hypothesis that genetic and environmental factors interact in the formation and transformation of polyps. An NCI grantee at Johns Hopkins has shown a specific set of genes at multiple sites are at work in colon cancer. These sites include 5Q, 17P and 18Q.

The occurrence of colon cancer has also been strongly associated with modern affluence, and indirect evidence -- largely based on differences in cancer rates between countries and changes in rates among migrants -- has implicated diet as potentially important. Indeed, it has been estimated that as much as 90 percent of colon cancer in the U.S. might be prevented by changes in diet. However, since the specific influence of diet has not yet been definitively identified from epidemiological investigations, it is not possible to issue preventative guidelines at this time. It appears that colon cancer almost certainly involves a strong interaction of genetics and environment. Without the necessary environment, few will develop colon carcinoma; but in a suitable environment, those with a genetic predisposition will be at high risk. Etiologic studies of colon cancer will become far more powerful when specific genetic markers for predisposition continue to emerge.

Mr. Porter. Again, briefly, what nutritional and diagnostic strategies does NCI recommend for an individual with a family history of colon cancer?

Dr. Broder. The hereditary form of colon cancer makes up five to 15 percent of all colon cancers. Most authorities estimate that five to six percent of colon cancer results from a dominant genetic trait. In this group, the disease occurs earlier on, average at age 44, and is more frequent on the right side of the colon (in the proximal colon). For this specific high-risk group, colonoscopy every year, beginning at 25 years of age, has been recommended. The U.S. Preventive Services Task Force recommends periodic colonoscopy for all persons with a history of familial polyposis.

Most persons with a family history of colon cancer do not belong to either of the above groups but these individuals should have closer surveillance than the normal person where the recommendation is fecal occult blood testing annually over age 50 and sigmoidoscopy every three to five years.

Results from recently published studies indicate that broader screening for colonic polyps is needed to further assess the evidence for genetically determined susceptibility to colorectal polyps and cancer. Current screening protocols should be adjusted to reflect genetic predisposition for colonic neoplasia. Greater emphasis should be placed on the recommendation that first-degree relatives of persons with colorectal cancer should undergo standard screening for colorectal cancer. In addition, first-degree relatives of persons with adenomatous polyps should also be screened. Future efforts will be directed at mapping the areas of genetic susceptibility to a specific portion of one or more chromosomes so that precise genotyping of persons at risk can be carried out. Once the susceptibility locus has been located and mapped, genetically susceptible persons who are affected with colorectal cancer can be compared to susceptible persons who are affected only with colonic polyps, and to both susceptible and nonsusceptible persons who are unaffected. These studies will determine the interaction of the susceptibility locus with environmental (dietary) risk factors.

Fiber-rich diets in human studies have indicated fairly consistently an association between an increase in fiber in the diet and a reduced risk of colon cancer. In the dietary guidelines published by NCI, the recommended fiber intake is 20 to 30 grams per day from a variety of food sources, including vegetables, fruits and whole grain cereals. An upper limit of 35 grams is suggested to avoid any possible adverse risk.

GENITOURINARY CANCERS

Mr. Porter. How much is NCI currently spending on researching genitourinary cancer?

Dr. Broder. NCI is currently spending approximately $40 million on research into kidney and urological disorders. NCI also supports an additional $17 million in cervical cancer research.

Mr. Porter. Do you coordinate these efforts with the NIDDK?

Dr. Broder. NCI participates on the Kidney, Urologic, and Hematologic Interagency Coordinating Committee, a congressionally mandated DHHS-wide committee.

CHRONIC FATIGUE SYNDROME

Mr. Porter. Is NCI conducting any research on the disorder Chronic Fatigue Syndrome (CFS)?

Dr. Broder. Yes. Since the isolation of human herpes virus-6 (HHV-6) in 1986, the association of this virus with various lymphoproliferative disorders, including CFS, has been studied. Various ongoing studies on CFS include: 1) the understanding of the relevance of HHV-6 antibody titers in CFS patients compared to healthy donors; 2) the detection of viral antigen-expressing cells using HHV-6 monoclonal antibodies in CFS patients and normal donors; 3) the testing of drugs that could block HHV-6 replication; 4) investigating an association of HHV-6 and human retroviruses; and 5) the study in Lake Tahoe region to determine whether CFS predisposes for cancer development.

Two of the NCI researchers involved with CFS studies are members of the National Advisory Council on CFS. This council is helping to coordinate a national effort on the study of the etiology and control of CFS.

Mr. Porter. Are you conducting any research which might be of potential benefit to CFS sufferers?

Dr. Broder. Yes. Preliminary results from one study indicate that antibody titers correlate with the degree of disease in the majority of the CFS cases. Thus a test for HHV-6 could be used as a diagnostic tool to monitor progression of CFS. In another study, antiviral drugs that could block HHV-6 replication, and therefore may be useful in the treatment of CFS patients, are being evaluated. In addition, clinical trials on CFS patients using immunoglobulin and interferon alpha 2A are being conducted. This work is preliminary and not ready for definitive conclusions.

CANCER AND OLDER AMERICANS

Mr. Young. Dr. Broder, last year we discussed your initiatives at the National Cancer Institute to reduce the risk of cancer in the older American population. Can you update the Committee on your progress in this regard and how much have you included in your 1991 budget request for this project?

Dr. Broder. Thank you for the question. NCI has inaugurated several key programs that focus on the older American population's cancer control problems and the best methods to address them. In some settings, Americans over 65 are in an underserved population.

In addition, ongoing epidemiology studies provide critical data about this population group because, whenever possible, epidemiologic analyses of specific cancers involve comparisons of risks by age group. These analyses are particularly important for those cancers whose incidence rates show a progressively upward trend with advancing age or striking predominance at older ages (e.g., multiple myeloma and prostate cancer). The age patterns for several cancers provide important insights into the role of cumulative environmental exposures, latency periods, multistage mechanisms, and intrinsic susceptibilities that may be associated with the aging process.

A particularly important study involves Swedish women who have used menopausal hormones of different formulations for many years. An excess risk of endometrial cancer (showing a dose-response with both duration of use and the strength of the medication) was noted for estrogens taken alone, without any progestational agents. For women who used only the combination regimen (i.e., estrogen plus progestogen), no excess risk was detected. Evaluation of breast cancer risk revealed a 60 percent increase in breast cancer after 10 or more years of replacement estrogen therapy. The cohort of women continues to be followed for a variety of hormonally-related events, including potential health benefits as well as risks.

In a study of vulvar/vaginal cancer which occurs predominantly among older women, major risk factors were found to be multiple sexual partners, smoking, absence of Pap smear screening, and a history of genital warts. In addition, other studies are investigating a broad range of exposures related to cancers of the breast, endometrium, and ovary among post-menopausal women.

Another prospective study is investigating health-related and lifestyle practices on a variety of cancers, including those of the breast, colon, and urinary tract among adults aged 60 years or older in a Los Angeles retirement community. It is expected that one outcome of this study will be an evaluation of the long-term risks and benefits of estrogen replacement therapy.

Skin cancer is the most frequent neoplasm among Caucasians in the United States, affecting at least 500,000 people annually. The frequency of non-melanoma skin cancers (i.e., basal cell and squamous cell carcinomas) is greatest in people over 65 years of age. A recent NCI study, performed in collaboration with a

Kaiser-Permanente HMO, suggests that the incidence rates for squamous cell carcinoma and melanoma of the skin have been increasing exponentially. Solar ultraviolet (UV) radiation has been implicated as the major etiologic agent responsible for various skin cancers, with trends in sunlight exposure being influenced by changing recreational activities and clothing patterns. In collaboration with other agencies, monitoring of UV surface levels and skin cancer incidence is continuing in an effort to clarify the potential effects of ozone layer depletion.

NCI is reviewing patterns of care data from nine grants funded between 1983 and 1987 under the Request for Application (RFA) mechanism to develop an action plan for identifying priority research areas that focus on the excess cancer mortality rates in people over 65. Preliminary results indicate that even when controlling for other related factors, elderly patients receive less appropriate care than younger patients for breast cancer. In response to this finding, intervention research will be supported to improve access to and application of state-of-the-art breast cancer screening, early detection, and treatment of breast cancer for older women.

Epidemiological data from the SEER Program are also being analyzed to determine the extent of differences between the stage of cancer and the age of the patient at the time of initial diagnosis. The results of these studies will be assessed in conjunction with the analysis of patterns of care for elderly patients.

In the past year, NCI has supplemented four Mammography Consortium grants to assess the impact of interventions for screening mammographies in older women. These supplements will test the effectiveness of various health promotion models such as economic incentives, interventions by physicians, and the use of mobile vans to increase mammography utilization among women 65 years and older. A forum on breast cancer screening in older women is scheduled to take place July 30 to August 2, 1990. Several issues and problems related to breast cancer screening in older women will be discussed including: the efficacy of mammography, physician breast exam, and breast self-examination in older women; the biology of breast cancer in older women; an economic model for breast cancer screening in older women; co-morbidity and functional status of older women; health promotion and breast cancer screening in older women; physicians' knowledge, attitude, and behavior with respect to breast cancer screening in older women; the demographics of aging; and issues in screening special populations.

Efforts are also underway to examine cancer control in older Black Americans. Several key differentials for cancer in the older Black population have been noted by an ad hoc working group of experts. The differences identified which affect cancer screening and control behavior include: diversity in the knowledge and attitudes about the disease; access to cancer care facilities; the impact of socio-economic factors on cancer control which differentially affect this population; and differences in barriers to receiving cancer care.

Prostate cancer is more prevalent in older males in general, and in Black men over 65 years of age in particular. In early clinical trials conducted by NCI's Medicine Branch, the drug suramin significantly improved the prognosis of prostate cancer inpatients who had exhausted other treatment regimens. Phase II clinical trials are currently underway to confirm these results at cancer centers with expertise in prostate cancer.

NCI is also involved in multiple activities to reach older Americans with its cancer prevention, early detection, and treatment messages. NCI's Office of Cancer Communications is developing a cancer education resource kit to be distributed to the American Association of Retired Persons' (AARP) vast volunteer network. Also, AARP, NCI, and Fox Chase Cancer Center are developing and testing a targeted smoking cessation program for people over 50. NCI's Breast Cancer Screening Education Initiative is focused on women over 50 and over 65 years of age, and a concurrent cervical cancer screening program is being planned to target this same audience. NCI is also supporting Prostate Cancer Screening Awareness Week, which emphasizes the need for screening in men over 40 years of age, with a special effort targeted toward minority men.

In patient education, information resources are being developed for the National Coalition of Cancer Survivors. Efforts are underway to make NCI's patient education publications readily available to older Americans and to increase their participation in NCI-sponsored clinical trials.

NCI is also developing collaborative activities with a sister NIH Institute, the National Aging Institute. Dr. Williams and I have discussed issues of mutual interest and benefit to older Americans from both the aging process and cancer process. We will continue to develop and expand our activities in this area.

Additionally, the Cancer Institute is in the process of announcing a Request for Applications (RFA) to study the underlying molecular, cervical and immunological factors in AIDS-related cancers. We expect to make several awards in this area.

NCI's FY 1991 budget request for these activities is estimated at $10 million.

PAP SMEARS

Mr. Young. Dr. Broder, recently I became aware of a case in my district where a woman was diagnosed with cervical cancer. What is most disturbing about this case is that she regularly had pap smears done that were consistently negative for the presence of cancer causing cells. Earlier today, you discussed efforts to improve the ability of doctors to read these test results. Can you tell the Committee what programs you have in place to prevent the misreading of test results, such as pap smears, and how you plan to disseminate this information to doctors and laboratories throughout our nation? Also, how frequently do you find cases where patients test negative but are later diagnosed with cancer?

Dr. Broder. While direct control of quality assurance in interpreting Pap smears at the Federal level rests with the Health Care Financing Administration, the NCI has also taken steps to ensure accuracy of cytology reporting in this area.

In December 1989, cytopathologists and representatives from national medical and other organizations met at a National Cancer Institute workshop to revamp cervical/vaginal cytology reporting. The participants unanimously agreed that the use of the current Papanicolaou classifications should be discontinued in favor of the newly devised Bethesda System. There was a consensus that the Papanicolaou classifications were obsolete, in that while smears designated as class 1 are normal and class 5 are malignant, there is no uniform interpretation of intermediate classes 2 through 4. In addition, Pap classifications do not provide diagnoses for noncancerous conditions, such as infections, which may be detected by Pap smears.

Therefore it was decided that the 1988 Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses should serve as a guideline for cytopathology reports of cervical/vaginal specimens. The Bethesda System uses clear, unambiguous diagnostic terms to describe infections and precancerous cell changes. It also reports on the adequacy of the cervical smear itself and identifies samples that are unsuitable for interpretation. The recognition of unsatisfactory smears can help to reduce the false-negative results that can occur in Pap smear evaluations.

According to the American College of Obstetrics and Gynecology (ACOG), between 15 percent and 40 percent of women who have cancer or precancerous conditions may have a Pap smear designated as normal. ACOG attributes half of the false negatives problem to clinician error in taking the sample and the other half to laboratory personnel error in reading the specimen.

A number of professional organizations have already indicated their support of the Bethesda System, including the International Academy of Cytology, the American Society of Cytology, the American Society for Cytotechnology, the College of American Pathologists, and the Planned Parenthood Foundation. NCI is preparing educational materials, including video tapes that can be used in continuing education programs for pathologists and cytotechnicians. By providing a uniform framework of diagnostic terminology, it is anticipated that the Bethesda System will become an important part of current efforts to improve quality assurance in cervical Pap smear screening. NCI views this as a very important activity.

NOVEL COMPOUNDS

Mr. Myers. Is there any research being conducted to examine the use of Tamoxifen in high-risk groups as a prevention of cancer?

Dr. Broder. The NCI is exploring a variety of possible new uses for tamoxifen in high-risk groups as a prevention for breast cancer. The Institute recently held a workshop to explore whether tamoxifen could be used for the prevention of breast cancer. There is no consensus in the scientific community on this point. Some doctors have expressed a concern that tamoxifen could cause a certain number of cancers in its own right (primarily cancers of the uterus). This theoretical risk -- and related risks -- has been a source of caution on the part of many advisors to the Institute. The NCI is currently providing support for a study which is evaluating the long-term effects of tamoxifen in post-menopausal node-negative breast cancer patients. The main goals of the study are to examine the effects of tamoxifen on bone density, calciotropic hormones and serum lipids and lipoproteins. The results of this study are very important since there is extensive use of tamoxifen as a post-operative adjuvant therapy (i.e., as a supplement to surgery) and its potential use as a preventive agent in women at a high risk of developing breast cancer. Preliminary evidence from the study suggests that tamoxifen may decrease a woman's risk of developing a second, new primary breast cancer. With a more comprehensive data base and longer follow-up of the critical and clinical effects of tamoxifen, it will then be possible to design and implement a clinical trial that will determine whether a tamoxifen intervention in high-risk women could prevent breast cancer and also provide knowledge about the mechanisms of carcinogenesis in human breast cancer. NCI staff are closely following certain clinical trials now underway in other countries, and are prepared to act promptly on any new data.

Mr. Myers. France has developed a birth control pill known as RU-486. The drug is viewed as a possible treatment for breast cancer, Cushing's Syndrome, and other diseases. Has this drug been examined here in the U.S. for its possible use as a treatment for these diseases?

Dr. Broder. The NCI supports basic research studies of the role of the progesterone receptor in breast cancer, including studies of the interaction of the antiprogestin RU-486 and the progesterone receptor. It is possible that the results of these studies will suggest new approaches for the treatment, diagnosis or prognosis of breast cancer.

Mr. Myers. Is the radiological pharmaceutical, Copper 67 still being examined as a possible early diagnosis tool for lymph nodes?

Dr. Broder. Copper-67 has been linked ("chelated") to a monoclonal antibody that recognizes a cell surface protein ("Lym-1") frequently found in human B-cell lymphomas and leukemias. In clinical evaluation, the Copper 67-Lym-1 conjugates specifically detected tumor nodules in animal models of human disease. No tumor visualization has been observed in normal tissues or tumors that do not express the Lym-1 protein on their surface.

The interest in Copper-67-labeled antibodies stems from the potential utilization of this agent for both detection and therapy of cancer. Copper-67 is a promising radioisotope because of its long half-life and ability to provide high doses of radiation particles to a very specific target. In addition, Copper-67 releases radioactive emissions suitable for imaging of human tumors. These emissions may permit calculation of delivered radiation dose from pre-therapy imaging studies. Therapeutic trials with Copper-67-labeled Lym-1 antibodies are planned.

CHERNOBYL

Mr. Myers. The Chernobyl accident in the Soviet Union has placed a great manly people with high doses of radiation. Is the National Cancer Institute working with or assisting the USSR in any way to help these victims?

Dr. Broder. The NCI has been able to assist and work with the Soviets in responding to the medical needs of the victims from the Chernobyl accident. Under the auspices of the U.S.-USSR Cancer Program through NCI, a clinical investigator from Johns Hopkins University traveled in 1987 to assist Soviet physicians at Moscow's All-Union Cancer Research Center (AUCRC) in autologous bone marrow transplantation techniques. Last year, two Soviet physicians were trained for a period of two months at Johns Hopkins University in an NCI-sponsored research program in bone marrow transplantation. As a result of this training, a bone marrow transplantation unit is now operational at the AUCRC in Moscow; these two visiting scientists are now the Director and Deputy Director of this unit.

In September 1989, two NCI investigators went to Kiev and Chernobyl to participate in a conference on the follow-up radiation effects of the nuclear accident. As a result of this meeting, a U.S.-USSR workshop on radiation-induced thyroid disease has been scheduled for November 12-17, 1990, in Kiev; two Soviet thyroid specialists will visit NCI this May to collaborate in planning the workshop. The November 1990 workshop will generate recommendations for follow-up studies of thyroid dysfunction among the people exposed to radiation from Chernobyl. Similar workshops should follow, concerning leukemia, child health, and epidemiologic methods.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

FY 1991 Budget — Page No.

Appropriation language and explanation of language change........ 38

Amounts available for obligation........ 39

Budget mechanism table........ 40

Crosswalk tables........ 42

Summary of changes........ 46

Budget authority by activity........ 47

Budget authority by object........ 48

Significant items in House and Senate Appropriations Committee reports........ 49

Authorizing legislation........ 57

Appropriations history........ 58

Justification:

A. General statement........ 59
B. Program accomplishments........ 63
C. AIDS research program........ 71
D. Cancer causation research........ 88
E. Detection and diagnosis research........ 107
F. Treatment research........ 112
G. Cancer biology research........ 130
H. Cancer centers support........ 144
I. Research manpower development........ 147
J. Construction........ 151
K. Cancer prevention and control........ 152
L. Detail of permanent positions........ 165
M. Advisory and assistance services........ 167

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

For carrying out section 301 and title IV of the Public Health Service Act with respect to cancer [$1,664,000,000] *$1,694,059,000*.

[Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1990.]

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE

Amounts Available for Obligation [1/]

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation...............	$1,593,536,000	$1,664,000,000	$1,694,059,000
Enacted administrative reduction.................	-21,657,000	-6,839,000	---
Sequester order.............	---	-22,829,000	---
Subtotal, adjusted appropriation...........	1,571,879,000	1,634,332,000	1,694,059,000
Real transfer to the Office of the Assistant Secretary for Health for AZT grants.	-1,530,000	---	---
Comparative transfers to:			
Fogarty International Center, NIH for passport activities................	-37,000	-38,000	---
Division of Research Resources, NIH for administration of RCMI program..................	-49,000	---	---
Comparative transfer from:			
Office of the Director, NIH for FTE increase......	2,616,000	---	---
Subtotal, adjusted budget authority.......	1,572,879,000	1,634,294,000	1,694,059,000
Unobligated balance lapsing.	-6,000	---	---
Total obligations...........	1,572,873,000	1,634,294,000	1,694,059,000

[1/] Excludes the following amounts for reimbursable activities carried out under this account: 1989 -- $4,829,000; 1990 -- $2,275,000; 1991 -- $2,491,000.

Excludes $640,000 for royalties received in 1989 and available in 1990.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Mechanism
(dollars in thousands)

	1989 Actual		1990 1/ Appropriation		1991 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants						
Research projects:						
Noncompeting	2,374	$558,057	2,353	$557,993	2,294	$591,434
Administrative supplemental	(114)	6,177	(140)	7,000	(140)	7,000
Competing:						
Renewal	324	85,645	359	99,915	361	95,733
New	402	73,081	407	83,539	454	90,519
Supplemental	2	49				
Subtotal, competing	728	158,775	766	183,454	815	186,252
Subtotal, research projects	3,102	723,009	3,119	748,447	3,109	784,686
Research centers:						
Basic research	15	19,577	15	19,918	15	19,940
Clinical/comprehensive	41	81,550	41	82,970	41	83,064
Subtotal, research centers	56	101,127	56	102,888	56	103,004
Other research:						
Research career program	123	7,640	123	8,323	123	8,323
Cancer education	44	2,983	29	2,942	29	2,942
Cooperative clinical research	171	60,152	189	59,747	189	59,747
Minority biomedical research support		2,793		2,582		2,801
Other research related	212	9,140	200	8,817	200	8,817
Subtotal, other research	550	82,708	541	82,411	541	82,630
Total, research grants	3,708	906,844	3,716	933,746	3,706	970,320

Training:						
Individual awards:						
Noncompeting	84	2,051	100	2,541	100	2,560
Competing:						
Renewal						
New	78	1,852	78	2,036	78	2,017
Subtotal, individual	162	3,903	178	4,577	178	4,577
Institutional awards:						
Noncompeting	1,123	25,786	761	20,424	1,116	28,090
Competing:						
Renewal	116	2,611	442	10,142	87	2,456
New	27	854	22	650	22	670
Subtotal, institutional	1,266	29,251	1,225	31,216	1,225	31,216
Total, training	1,428	33,154	1,403	35,793	1,403	35,793
Research and development contracts	383	187,284	394	198,099	394	201,796
	FTEs		FTEs		FTEs	
Intramural research	1,613	296,397	1,682	314,679	1,721	333,219
Research management and support	422	72,630	432	72,027	432	75,993
Cancer prevention and control	138	74,100	148	74,944	155	75,459
Construction		2,470		5,006		1,479
Total, NCI	2,173	1,572,879	2,262	1,634,294	2,308	1,694,059
HIV/AIDS	(188)	(124,148)	(281)	(150,304)	(300)	(160,807)

1/ Includes approximately $3,527,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

CROSSWALK - 1989 Actual

(dollars in thousands)

	Research Grants			Training							
	Research Projects	Research Centers	Other Research	Indiv-idual	Instit-utional	R&D Contracts	Intra-mural Research	Research Mgmt & Support	Cancer Prev. & Control	Constr-uction	Total
Research:											
Cancer causation..	$258,891		$4,041			$76,242	$78,124	$19,121			$436,419
Detection and diagnosis research...	72,450					12,881	18,689	6,188			110,208
Treatment research...	196,832		60,229			91,983	138,990	23,978	$459		512,471
Cancer biology....	194,836		7,815			5,948	60,594	14,037			283,230
Subtotal.....	723,009		72,085			187,054	296,397	63,324	459		1,342,328
Resource Development:											
Cancer centers support....		$101,127				230		1,070			102,427
Research manpower development			10,623	$3,903	$29,251			2,770			46,547
Construction.								261		$2,470	2,731
Subtotal.....		101,127	10,623	3,903	29,251	230		4,101		2,470	151,705
Cancer prevention and control.								5,205	73,641		78,846
Total, NCI...	723,009	101,127	82,708	3,903	29,251	187,284	296,397	72,630	74,100	2,470	1,572,879

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

CROSSWALK - 1990 Appropriation 1/

(dollars in thousands)

	Research Grants			Training							
	Research Projects	Research Centers	Other Research	Indiv-idual	Instit-utional	R&D Contracts	Intra-mural Research	Research Mgmt & Support	Cancer Prev. & Control	Constr-uction	Total
Research:											
Cancer causation..	$266,519		$3,886			$79,459	$78,735	$18,797			$447,396
Detection and diagnosis research...	76,868					14,136	19,737	6,168			116,909
Treatment research...	208,478		59,837			98,446	153,324	23,614	$457		544,156
Cancer biology....	196,582		7,423			6,058	62,883	13,762			286,708
Subtotal.....	748,447		71,146			198,099	314,679	62,341	457		1,395,169
Resource Development:											
Cancer centers support....		$102,888						1,541			104,429
Research manpower development			11,265	$4,577	$31,216			2,675			49,733
Construction.								159		$5,006	5,165
Subtotal.....		102,888	11,265	4,577	31,216			4,375		5,006	159,327
Cancer prevention and control.								5,311	74,487		79,798
Total, NCI...	748,447	102,888	82,411	4,577	31,216	198,099	314,679	72,027	74,944	5,006	1,634,294

1/ Includes approximately $3,527,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

CROSSWALK - 1991 Estimate

(dollars in thousands)

	Research Grants			Training							
	Research Projects	Research Centers	Other Research	Indiv-idual	Instit-utional	R&D Contracts	Intra-mural Research	Research Mgmt & Support	Cancer Prev. & Control	Constr-uction	Total
Research:											
Cancer causation..	$281,959		$3,873			$82,650	$81,564	$19,945			$469,991
Detection and diagnosis research...	79,276					14,442	21,006	6,641			121,365
Treatment research...	216,433		59,834			98,531	163,962	24,990	$473		564,223
Cancer biology....	207,018		7,658			6,173	66,687	14,290			301,826
Subtotal.....	784,686		71,365			201,796	333,219	65,866	473		1,457,405
Resource Development:											
Cancer centers support....		$103,004						1,584			104,588
Research manpower development			11,265	$4,577	$31,216			2,821			49,879
Construction.								166		$1,479	1,645
Subtotal.....		103,004	11,265	4,577	31,216			4,571		1,479	156,112
Cancer prevention and control.								5,556	74,986		80,542
Total, NCI...	784,686	103,004	82,630	4,577	31,216	201,796	333,219	75,993	75,459	1,479	1,694,059

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Research Programs Summary

[dollars in thousands]

	1989 Actual	1990 Appropriation	1991 Estimate	Increase or Decrease
Epidemiology........	$91,372	$95,067	$98,478	+$3,411
Carcinogenesis [physical & chemical]	169,673	169,913	177,320	+7,407
Biological carcinogenesis.....	152,571	152,320	163,601	+11,281
Nutrition...........	36,650	43,612	46,100	+2,488
Tumor biology.......	175,249	177,986	188,446	+10,460
Immunology..........	107,981	108,722	113,380	+4,658
Diagnostic research.	98,950	105,890	110,462	+4,572
Preclinical treatment research.	270,303	280,859	290,759	+9,900
Clinical treatment research.	236,959	257,227	264,373	+7,146
Rehabilitation research...........	2,620	3,573	4,486	+913
Total, research.....	1,342,328	1,395,169	1,457,405	+62,236
Resource Development	151,705	159,327	156,112	-3,215
Cancer Prev. & Control	78,846	79,798	80,542	+744
Total, NCI..........	1,572,879	1,634,294	1,694,059	+59,765

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Summary of Changes

1990 Estimated Budget Authority	$1,634,294,000
1991 Estimated Budget Authority	1,694,059,000
Net Change	+59,765,000

	1990 Current Estimate Base		Change from Base	
	Pos. (FTEs)	Amount	Pos. (FTEs)	Budget Authority
Changes:				
A. Built-in:				
1. Within grade increase		$128,822,000		+$714,000
2. January 1991 payraise		128,822,000		+3,735,000
3. Annualization of January 1990 pay raise		128,822,000		+1,120,000
4. One extra day of pay		128,822,000		+494,000
5. Federal Employees Compensation Fund		445,000		+15,000
6. Unemployment compensation increase		210,000		+7,000
7. FTS rate increase		1,871,000		+59,000
8. Increased cost of centrally furnished services		119,409,000		+8,364,000
9. Increased cost of laboratory supplies, materials and other expenses		120,386,000		+4,717,000
10. Service and Supply Fund		31,345,000		+1,034,000
11. DHHS Working Capital Fund		1,424,000		-70,000
Subtotal				+20,189,000
B. Program:	No.	Amount	No.	Amount
1. Research project grants:				
a. Noncompeting	2,353	564,993,000	-59	+33,441,000
b. Competing	766	183,454,000	+49	+2,798,000
Total	3,119	748,447,000	-10	+36,239,000
2. Research centers		102,888,000		+116,000
3. Other research		82,411,000		+219,000
4. R&D contracts		198,099,000		+3,697,000
	Pos. (FTEs)		Pos. (FTEs)	
5. Intramural research	1,682	314,679,000	+39	+2,089,000
6. Research management & support	432	72,027,000		+743,000
7. Cancer prevention & control				
a. Intramural	148	13,318,000	+7	+350,000
b. Extramural		61,626,000		-350,000
8. Construction		5,006,000		-3,527,000
Subtotal			+46	+39,576,000
Total changes			+46	+59,765,000

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Authority by Activity

[dollars in thousands]

	1989 Actual		1990 1/ Appropriation		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Research:						
Cancer causation.......	627	$436,413	647	447,396	659	$469,991
Detection & diagnosis research.............	156	110,208	162	116,909	163	121,365
Treatment research.....	736	512,471	787	544,156	799	564,223
Cancer biology.........	432	283,230	444	286,708	451	301,826
Subtotal, research.....	1,951	1,342,322	2,040	1,395,169	2,072	1,457,405
Resource Development:						
Cancer centers support.	12	102,427	12	104,429	17	104,588
Research manpower development...........	29	46,547	29	49,733	29	49,879
Construction...........	3	2,731	3	5,165	3	1,645
Subtotal, resource development...........	44	151,705	44	159,327	49	156,112
Cancer prevention and control...........	178	78,846	178	79,798	187	80,542
Subtotal, obligations..	2,173	1,572,873	2,262	1,634,294	2,308	1,694,059
Unobligated balance lapsing...............		+6		---		---
Total, budget authority	2,173	1,572,879	2,262	1,634,294	2,308	1,694,059
HIV/AIDS...............	(188)	(124,148)	(281)	(150,304)	(300)	(160,807)

1/ Includes approximately $3,527,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Total number of full-time permanent positions......	1,781	1,815	+34
Total compensable workyears:			
Full-time equivalent employment............	2,333	2,379	+46
Full-time equivalent of overtime and holiday hours	30	30	---
Average ES salary..........	$76,219	$91,462	+15,243
Average GM/GS grade........	10.07	10.07	---
Average GM/GS salary.......	$36,354	$37,662	+1,308
Average salary, grades established by act of July 1, 1944 [42 USC 207]	$66,269	$68,655	+2,386
Average salary ungraded positions.......	$21,621	$22,400	+779
Personnel compensation:			
Full-time permanent.......	$70,422	$73,024	+2,602
Other than full-time permanent................	24,140	25,295	+1,155
Other personnel compensation	4,828	5,269	+441
Special personal services payments........	10,094	13,370	+3,276
Total personnel compensation	109,484	116,958	+7,474
Personnel benefits.........	19,338	20,663	+1,325
Benefits to former personnel	100	200	+100
Travel and transportation of persons................	5,500	5,500	---
Transportation of things...	1,500	1,500	---
Communications, utilities, and rent..................	10,000	10,000	---
Printing and reproduction..	4,000	4,000	---
Other services:			
Project contracts.........	235,199	238,411	+3,212
Centrally furnished services	115,929	123,049	+7,120
Standard level user's charge	3,480	4,724	+1,244
Other.....................	91,764	97,943	+6,179
Supplies and materials.....	32,000	32,000	---
Equipment..................	10,000	10,000	---
Grants, subsidies, and contributions.........	995,998	1,029,109	+33,111
Interest...................	2	2	---
Total authority by object.	1,634,294	1,694,059	+59,765

National Cancer Institute

Significant Items in House and Senate Appropriation Committee Report

	Item FY 1990 House Report	Action Taken or To Be Taken
1.	"Disparity in cancer rates between certain minorities and the general population is widening... It is important that the causes of these disparities be defined and that the NCI do whatever it can to reverse this trend... Where possible, support for additional and accelerated activities aimed at improving cancer statistics in minorities and the economically disadvantaged, including the rural poor is encouraged." (page 51)	During FY 1991, NCI plans an expansion of the Surveillance, Epidemiology and End Results (SEER) program to add an increased statistical base for Black Americans and Hispanics. Because the full spectrum of cancer incidence and mortality for rural areas is not known, NCI also plans to increase coverage of people who live in rural areas, particularly rural agricultural areas, within the SEER program.
2.	"In mid-January, the NIH and the FDA approved a proposal by NCI and National Heart, Lung, and Blood investigators to transfer a foreign gene into host defense cells -- so called tumor infiltrating lymphocytes (TILs)... The Institute is encouraged to determine whether these approaches can lead to practical new treatments." (page 52)	Preliminary analysis of the first clinical trial of adoptive immunotherapy using human cells that carry foreign genes indicates that the procedure has been successful. Future studies will examine the insertion of additional genes into these host defense cells to further enhance their antitumor activity. NCI will continue to explore this new treatment avenue which may prove applicable to diseases such as sickle cell anemia and cystic fibrosis.
3.	"The NCI has developed a comprehensive program of information dissemination activities, as part of the Institute's efforts to reduce cancer mortality... Innovative ways of expanding information dissemination should be explored." (page 53)	NCI will continue its efforts to broadly disseminate advances in cancer treatment and prevention to the medical community and will examine new ways to accomplish this goal so that the American public can benefit from new knowledge in these areas as quickly as possible.

Item FY 1990 House Report	Action Taken or To Be Taken
4. "The NCI is committed to continuing efforts to increase usage of the Physicians Data Query (PDQ) system, a computerized data base that lists treatment options and available clinical protocols for all types of cancer. Other ways for enhancing physician and patient education should be explored." (page 53)	NCI will continue to explore innovative ways in which physicians and the public can access the PDQ database. A patient education network has been established in conjunction with clinical and comprehensive cancer centers. NCI is also working with the National Coalition for Cancer Survivorship to develop an information resource for cancer survivors and their families that addresses health and other key topics such as employment, nutrition and pain management.
5. "The Institute is encouraged to seek innovative ways to increase the pool of scientists available for clinical investigative work and to give special attention to the training of minorities underrepresented in cancer research and therapy." (page 53)	NCI has intensified efforts to recruit and train underrepresented minorities through National Research Service Award-supported institutional training grants. Grantees are required to complete Minority Recruitment Plans which outline how increases in the number of minority students supported through these training grants will be achieved. NCI staff also plans to utilize the program supporting student research laboratory experiences to increase minority participation.
6. "The Committee urges the Institute to continue to expand its research initiatives related to minorities." (page 53)	NCI has taken steps to issue an Request for Application (RFA) on cancer prevention and clinical research in underserved populations. The goal is to stimulate the establishment and implementation of a program to integrate and deliver comprehensive cancer prevention, screening, and early detection and treatment services to high-risk minority, low income and other underserved persons.

	Item FY 1990 Senate Report	Action Taken or To Be Taken
1.	"The Committee is concerned with reports of high cancer rates in rural agricultural areas. In order to develop more specific information upon which to base intervention strategies, the National Cancer Institute has been directed to develop a focused statistical series on cancer in rural agricultural areas. This series would be added to NCI's Surveillance Epidemiological and End Results survey which currently reports cancer incidence rates on a county-by-county basis." (page 39)	In its report to the Committee entitled "Statistical Series on Cancer in Rural Areas", the NCI states that there is a definite need to more fully examine the scope and extent of cancer incidence and mortality in rural agricultural areas. There will be an expansion of NCI's Surveillance, Epidemiology and End Results (SEER) program to provide increased coverage of people who live in rural areas, particularly rural agricultural areas. A special task force will be appointed to review the current data on cancer in rural areas and make recommendations to the Institute for additional research initiatives.
2.	Additional studies are needed to provide early data to support expansion of adult clinical trials to the pediatric population. Expansion of clinical trials in the pediatric AIDS population poses problems not experienced in the adult clinical trial studies. More resources are needed to carry out pediatric clinical trials specifically for ancillary requirements associated with children and adolescents." (page 50/51)	NCI scientists will continue to conduct clinical protocols testing new leads as they emerge from the AIDS Drug Discovery Program in adults and children who are symptomatic for HIV infection. Clinical and laboratory testing of AZT will continue, along with new studies using ddC and ddI.

	Item FY 1990 Senate Report	Action Taken or To Be Taken
3.	"The Committee is very supportive of programs within the NCI which will greatly enhance the success of treating tumors otherwise inoperable. As a result, such programs like proton beam therapy should be fully explored so that the best and most effective treatments are available throughout the Nation." (page 109)	NCI has issued a Request for Applications to solicit grant proposals for planning and development activities in proton beam therapy. A small number of state-of-the-art hospital-based proton research and treatment facilities will conduct trials to determine if proton beam therapy is superior to conventional x-ray therapy in terms of morbidity and outcome for a variety of tumors.
4.	"The Committee is concerned... that the death rates for those over 65 have not diminished and cancer mortality rates are disproportionately high for blacks and certain minorities as they compare to the general population. The Committee finds this disparity unacceptable and urges NCI to continue to address this issue by strengthening existing programs and developing new minority-related initiatives. In this regard the Committee notes that NCI supports promotional efforts to increase minority use of the Cancer Information Service [CIS], a national toll-free cancer information network. Moreover, NCI program initiatives include the Black leadership initiative through which six regional coordinators will be appointed by NCI to assist in the education of minority groups in health prevention techniques to reduce their risk of cancer. The NCI should expand its activities to examine the causes of the disparity in cancer rates by age and race and take steps to correct this problem, where possible, and continue its	Intervention research programs are being developed to address the severe and excessive cancer burden prevalent among older persons, low income persons, inner city residents and other medically underserved groups. Future efforts will be directed at identifying deficiencies in the medical/health care system that deter these groups from fully utilizing available health resources. A Cancer Prevention and Clinical Research in Underserved Populations program will be developed to integrate and transfer a full spectrum of cancer prevention, screening and early detection, and treatment results to high-risk minority and low-income groups.

	Item FY 1990 Senate Report	Action Taken or To Be Taken
	activities aimed at improving cancer statistics for the economically disadvantaged, including the rural poor." (page 109)	
5.	"The Committee is particularly aware that according to the NCI statistics, native Hawaiians have a significantly disproportionate incidence of certain types of cancer... To date, NCI has been unable to commit significant resources targeted toward the native Hawaiian population. The Committee feels that the time has come for NCI to make native Hawaiians and other Pacific islanders a significant priority in educational campaigns to reduce the unacceptably high mortality rate among this population." (page 109)	NCI has developed research projects to address cancer control problems among the Native American populations, including Hawaiian natives. Cancer control networks are being established among Hawaiian native populations that are modeled after the existing cancer control network for Black Americans. Current data sets are being used and new data sets are being developed to identify the cultural, spiritual, historical, and language barriers that contribute to delays in seeking prompt diagnosis and treatment among this population.

	Item FY 1990 Senate Report	Action Taken or To Be Taken
6.	Prevention and control -- "...The Committee encourages increased emphasis on prevention research and recognizes that a nutrition and cancer research laboratory is invaluable to this effort... The Committee is concerned with the lack of uniformity of state-of-the-art treatment for cancer patients across the United States and plans to continue to explore new ways to reach populations with the newer treatments and more effective diagnostic and early detection techniques." (page 110)	NCI's intramural Laboratory for Nutritional and Molecular Regulation will continue its ongoing investigations into the possible interactions between energy intake (calories) early in life and cancer development. NCI will continue to promote access to both clinical treatment research and cancer control research studies in the areas of early detection and screening, patient management, continuing care, and rehabilitation for community cancer specialists, primary care physicians, and other health care professionals to ensure that all cancer patients can avail themselves of state-of-the-art cancer therapies.
7.	"Cancer centers are an extremely valuable resource in NCI's comprehensive cancer program which perform basic cancer research, disseminate information, transfer technology, and apply the latest scientific findings to their communities. They also conduct prevention, control and therapy activities. The Committee urges the NCI to explore innovative ways to strengthen the centers program to improve the accessibility to state-of-the-art treatment for all Americans. The Committee is well pleased with the study prepared on the subject of cancer centers by the Institute of Medicine.... The study makes a series of recommendations regarding administrative arrangements for the cancer center program within the NCI. The Committee urges the NCI management to give careful and favorable attention to these recommendations...the	As a result of the recommendations from the Institute of Medicine's study entitled "Report on a Stronger Cancer Centers Program", NCI is currently in the process of developing a strategic plan to serve as a guide for the future expanded role of cancer centers to accelerate both the pace of cancer research and the transfer of new therapies from research settings into widespread clinical practice.

	Item FY 1990 Senate Report	Action Taken or To Be Taken
	Committee is concerned that in view of the important role played by cancer centers that five such centers may be defunded during fiscal year 1990. The Committee has added funds to the NCI budget to help ensure that the number of cancer centers remain constant in fiscal year 1990." (page 110)	
8.	The Committee is pleased that federally supported cancer research scientists have made significant advances in cancer treatment research.... The Committee is concerned, however, that due to low enrollment in clinical protocols, the lack of third-party coverage for patient care costs for clinical trial participants and the slow process by which new treatment ideas or drugs are made available for general use, more effective cancer treatment regimens for use by the general public are being restricted. The Committee expects to hear from NCI before the hearings next year on NCI recommendations to address these problems." (page 111)	In its report to the Committee entitled "Ways to Enhance the Widespread Application of Treatment Advances", NCI discusses the progress that has been made in the Institute's efforts to increase accrual to clinical trials nationally. The report also addresses the important issue of the growing reluctance of private third-party payers to provide reimbursement for the non-research, clinical care costs of cancer clinical trials and stresses that these policies threaten NCI's ability to enroll patients onto clinical trials, thereby denying them access to state-of-the-art treatments.

	Item FY 1990 Senate Report	Action Taken or To Be Taken
9.	"The Committee again urges the NCI to continue its systematic efforts to ensure that professional nurses are actively involved in the programs, advisory boards, and committees of NCI. In this regard, the Committee is especially pleased to learn that NCI is in the process of recruiting nurses to fill a position on the NCI Board of Scientific Counselors, and that the cancer centers, cooperative groups, and oncology programs clinical groups now have nursing committees to facilitate and develop research. Further, the Committee reiterates its support for NCI giving priority to the Nursing Oncology Individual Research Fellowship Award Program, the nursing clinical training programs, and the implementation nursing research initiatives. The Committee was especially pleased to note that the NCI Nurse Oncology Training Program, which began in 1985, has already more than doubled the number of baccalaureate nurses who are involved in oncology." (page 110)	NCI will continue to actively promote the participation of professional nurses on Institute committees and advisory boards as well as continue its support of nursing oncology research and nurse clinical training programs.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1990 Amount Authorized	1990 Current Estimate	1991 Amount Authorized	1991 Budget Estimate
Research and Investigation....	Section 301	42§USC241	Indefinite		Indefinite	
National Cancer Institute.........	Title IV, Part A (Sec. 408 (a)(1)(A))	42§USC284c	Such sums as necessary	$1,598,501,000	Authorizing legislation to be requested	$1,658,266,000
	(Sec. 408 (a)(1)(B))		Such sums as necessary	[1,523,557,000]	Authorizing legislation to be requested	[1,582,807,000]
			Such sums as necessary	[74,944,000]	Authorizing legislation to be requested	[75,459,000]
National Research Service Awards...	Section 487	42§USC288	Such sums as necessary 1/	35,793,000	Authorizing legislation to be requested 1/	35,793,000
Total, Budget Authority				$1,634,294,000		$1,694,059,000

1/ This training authority is shared with other research training programs of the National Institutues of Health and the Alcohol, Drug Abuse, and Mental Health Administration.

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Appropriations History

	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation[1]
1981........	982,901,000	993,600,000	988,284,000	989,355,000
1982........	902,832,000[2]	1,030,356,000	1,034,180,000	986,617,000
1983........	955,449,000	981,441,000	985,711,000	987,618,000
1984........	986,681,000	1,044,868,000[3]	1,062,017,000[3]	1,093,018,000
1985......	1,101,069,000	1,084,950,000[4]	1,187,693,000	1,196,528,000
1985 Proposed Recission..	-4,362,000	---	---	---
1986........	1,126,012,000	1,221,590,000[5]	1,271,555,000	1,258,159,000
1986 Sequester				-53,868,000
1986 Proposed Recission..	-6,800,000	---	---	---
1987[6]......	1,158,089,000	1,346,751,000	1,397,250,000	1,402,837,000
1987 Proposed Reappropr	[64,112,000]	---	---	---
1988........	1,302,823,000	1,448,411,000[8]	1 ,527,054,000	1,469,327,000
1988 Proposed Advan Appropr	508,294,000[7]	---	---	---
1989........	1,468,256,000[9]	1,593,536,000	1,591,036,000	1,571,879,000
1990........	1,494,741,000[10]	1,652,666,000	1,668,473,000	1,657,161,000[11]
1990 Sequester				-22,829,000
1991........	1,694,059,000			

[1] Reflects enacted supplementals, rescissions and reappropriations.

[2] Reflects the September Amendment; the original request was $1,025,941,000.

[3] Excludes $23,861,000 in NRSA training programs not considered.

[4] Excludes $89,153,000 for NRSA training programs, cancer control and construction activities not considered.

[5] Excludes $37,358,000 for construction activities and NRSA training programs not considered.

[6] The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House Allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate Allowance and the Appropriation spread the funding among the Institutes, including $61,674,000 for NCI.

[7] Proposed advanced appropriation to cover the continuation costs of competing research project grants awarded in 1988.

[8] Excludes funding for AIDS research. Proposed to be at the OASH level.

[9] Excludes funds for AIDS research & education [$125,280,000] proposed for consolidation in the Office of the Assistant Secretary for Health.

[10] The 1990 request excludes funds for the National HIV Program [$151,332,000] proposed for consolidation in the Office of the Assistant Secretary for Health.

[11] Excludes enacted administrative reduction of $6,839,000.

Justification

National Cancer Institute

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
TOTAL....	2,262	$1,634,294,000	2,308	$1,694,059,000	46	$59,765,000
AIDS.....	(281)	($122,247,000)	(300)	($150,304,000)	(19)	($28,057,000)

General Statement

The National Cancer Institute is dedicated to generating knowledge and applying it quickly in response to the challenge of a disease which causes death and suffering beyond metaphor: cancer. The intramural and extramural research programs are national resources of the highest quality. Today's challenge is to maintain the high quality of research and increase the speed of dissemination of research results and the transfer of research technology to clinical care. These efforts require creative, highly skilled scientists and clinicians, well equipped laboratories, but also when appropriate technological support at the cutting edge. The success of our mission requires other resources as well, such as a network of NCI Cancer Centers. NCI Cancer Centers are poised to address contemporary national and regional problems. Success also requires an array of organized clinical trials. The NCI program of clinical trials, both in treatment and prevention, generates knowledge regarding new drugs and therapies, while at the same time providing state-of-the-art care to individual patients. A vigorous program of treatment and prevention clinical trials must involve academic centers and community physicians; it must also effectively reach minorities, the poor, the aged, and the underserved populations of the nation. These are substantial challenges.

Science and the scientific method must underlie every activity of the NCI. In this regard, this has been a year of high achievement at the National Cancer Institute.

Illustrating the extraordinarily high quality of contemporary cancer research, two NCI scientists (together with a colleague from the National Heart, Lung, and Blood Institute) made medical history last Spring by inserting new genetic material into human cells (involved in the body's defenses against cancer) in the laboratory, returning the cells back to the patient, and demonstrated the presence of the gene-engineered cells in the patient's circulatory system two months later. These experiments are the legacy of prior NCI research that uncovered the body's mechanisms for killing cancer cells. These gene transfer experiments provide the basis for future gene therapies.

Fortunately, new treatments drawn from basic research are already reaching cancer patients. Using techniques developed from genetic engineering, there is increased ability to diagnose cancer at its earliest, most treatable stage. The NCI is developing more effective strategies for attacking cancer cells when they exist as microscopic deposits, instead of waiting for a cancer to fully express itself. This approach is often combined with surgery and is called adjuvant therapy.

For example, this year, scientists showed that significant reductions in cancer deaths from a type of advanced colon cancer could be achieved with this approach. Recently clinical trials showed that adjuvant treatment with an immune stimulant, levamisole, enhanced the effectiveness of 5-fluorouracil (5-FU) in treating Dukes' C colon cancer. There will be approximately 110,000 new cases of colon cancer in 1990 and about 21,000 will have Dukes' C (cancer confined to the bowel and adjacent lymph nodes). Although surgery is the first treatment, microscopic tumor deposits can remain in lymph nodes after surgery. Dukes' C patients are at high risk of recurrence and death, and this adjuvant treatment can make a significant difference in five-year survival rate, and reduce these deaths by a third. There is also success in understanding and combating the phenomenon of drug resistance, which can render cancers impervious to chemotherapy.

Advances are not all in the future, treatments are getting better right now for cancer patients. There are new drugs, new combinations of drugs and new radiotherapeutic and surgical methods, and the new biologically based immunotherapies.

Support for the value of adjuvant treatment, already mentioned, came out of NCI-supported clinical trials. Trials in the last year have shown hormonal treatment or chemotherapy after surgery, for certain kinds of breast and colon cancer can prolong disease-free survival and ultimately save lives. Newer studies are testing the concept of neoadjuvant therapy. This involves giving specific chemotherapy or radiotherapy before surgery. Sometimes this approach makes it possible to limit the severity of any functional impairment necessitated by the surgery, permitting the salvage of structures such as the bladder or rectum.

The speed with which new treatments are tested often hinges on accrual to clinical trials. It takes time to accrue patients to trials, time that must be added to that needed to test a hypothesis. NCI has organized large Clinical Cooperative Groups to confront this problem and speed clinical trials to their research conclusions. The Clinical Cooperative Groups now enroll about 27,000 patients per year on therapeutic studies. Because of the benefit to both patients and to research per se, NCI is using the mass media to bring clinical trials directly to the attention of the medical professions and the public. This speed is particularly important in minority populations which tend to have limited access to clinical trials and state-of-the-art therapy.

Today NCI has an intensified program of research technology transfer and community outreach and is committed to making the results of its research available and accessible to all Americans regardless of their race, age, income, social status, or place of residence. A network of NCI programs and facilities -- the SEER cancer surveillance program, Cancer Centers, the Community Clinical Oncology Program (CCOPs), the Cooperative Group Outreach Program (CGOPS), the Cancer Information Service (CIS), the Physician Data Query and outreach mechanisms (e.g. the Group C category for drugs, which allows physicians to prescribe new and effective drugs outside of clinical trials prior to Food and Drug Administration approval) transfers laboratory findings to clinical practice.

Recent SEER data emphasize that minority groups, the poor, the underserved and those over 65, have disproportionately high rates of cancer mortality or some special problems in terms of access to state-of-the-art medical care. In response, NCI has made reduction of cancer mortality in these groups priority issues. To help reduce cancer deaths among minority groups, the National Black Leadership Initiative on Cancer (NBLIC) has been incorporated into the NCI program. The NBLIC has mobilized black community-based and national leaders to spread the word about early detection and prevention of cancer in their regions.

NCI conducts national educational programs to encourage individuals to make health promoting changes in lifestyle, including improved diets and avoidance of smoking, or to seek screening check-ups for cancer at recommended intervals. NCI is working with supermarkets in minority areas to expand its successful supermarket-diet education program.

NCI has a successful drug development program in which natural products are gathered from all over the world and tested for activity against cancer and AIDS. These compounds are submitted by universities and drug companies to NCI laboratories where sophisticated laboratory studies are done and preclinical work is carried out at an exhaustive level. This program provides the public interest equivalent of a modern pharmaceutical company for the development of drugs for cancer and AIDS with significant applications of the Federal Technology Transfer Act.

Occasionally an old drug is used in a new way. Suramin, a drug long used for treating parasitic infections, is the first drug to have been found active in treating advanced prostate cancer, where the prostate cancer has progressed to a metastatic stage and attempts to treat it with hormones have failed. There will be about 106,000 cases of prostate cancer this year in the United States. This drug specifically inhibits a class of growth factors that stimulate the development of prostate tumors. This approach, using growth factor inhibitors, is being expanded to treatment of other types of solid tumors and leukemias.

NCI has worked over the past year with the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS chaired by Louis Lasagna, M.D. This Committee was constituted by the President's Cancer Panel at the request of then Vice President George Bush. The Committee has addressed the development of endpoints for New Drug Application (NDA) approval for cancer and AIDS drugs, and third party payments for routine medical care given in the context of clinical trials. Current federal and private insurance policies explicitly deny payment for the treatment of patients on clinical trials. The Committee will be issuing a report this Spring.

NCI has established an NCI/FDA fellowship training program in drug development and regulatory medicine. This will help to fill the growing need for physicians trained in drug development and clinical trials methodology.

A foundation stone of the National Cancer Program, the Cancer Centers Program is undergoing review, with new guidelines for comprehensive status being evolved. In order to plan for the future, NCI is developing a five-year plan in collaboration with representatives of centers and the National Cancer Advisory Board. NCI support is valuable to the cancer centers in building efficient, coordinated, well-staffed, well-equipped programs of basic and applied cancer research in communities across the country. The core grants provide specialized resources such as centralized facilities to stock pharmaceuticals and biologicals under study or being used in clinical trials, and centralized biotechnology facilities.

NCI uses new technology to advance research wherever possible. The NCI supercomputer facility at the Frederick Cancer Research Facility (FCRF) has now been operational for three years. It provides high-speed computing to scientists from NCI, NIH and the Department of Health and Human Services as well as to extramural scientists. Currently there are 400 registered users of the supercomputer and it is used to capacity. The supercomputer is very useful in structural analysis of drugs and macromolecules and in the analysis of gene sequences on genes of humans and viruses.

The NCI is unified and diverse at the same time. The interconnections between Divisions, between areas of study, between basic research and clinical application create an organic whole. None would be as productive without the other. In ways that are not always obvious, each research program needs the other for vitality. Basic laboratory research and epidemiologic studies revitalize our prevention and treatment approach, new drug development encourages early screening, early screening yields better therapy, novel advances in therapy stimulate more basic research.

Overall Budget Policy

The FY 1991 budget request for the National Cancer Institute is $1,694,059,000, an increase of $59,765,000 over the 1990 comparable amount.

This budget ensures a stable source of funds for cancer research and favors basic research. Most extramural mechanisms are held at approximately the FY 1990 level, with the exception of research project grants. The current request for research project grants increases by 4.8 percent over 1990. This will allow NCI to support 49 more competing research project grants and provide for average cost increases.

Program Accomplishments

This year two NCI-supported scientists, Drs. J. Michael Bishop and Harold E. Varmus, won the 1989 Nobel prize in Medicine. As young scientists, they did research in the intramural program at the NIH and today they hold NCI Outstanding Investigator Grants. In 1976, they published the remarkable conclusion that the oncogene in the virus did not represent a true viral gene, but instead was a normal cellular gene, which the virus had acquired during replication in the host cell, thus showing that oncogenes can arise from normal growth-regulating genes. This advanced understanding of tumor development illuminated virtually all biologic research and laid the groundwork for rational prevention and therapy.

Another 1989 Nobel laureate, Dr. Thomas Cech held an NCI Career Development Grant between 1980 and 1984. Dr. Cech of the University of Colorado and Dr. Sidney Altman of Yale University were jointly awarded the 1989 Nobel Prize for Chemistry on October 13. Working independently, Cech and Altman discovered that RNA can act as a true enzyme when it was previously believed that only proteins could carry out enzymatic functions.

A recent NCI-supported prevention study showed that a high wheat fiber supplement decreased the number of large bowel polyps, which are cancer precursors, among patients with familial adenomatous polyposis. Such patients are at extreme risk of acquiring large bowel cancer. This may allow development of practical prevention strategies not only for uncommon familial conditions, but for the general public.

Not only are prospects brighter for prevention, but it is increasingly possible to find people at high risk for cancer and to actively intervene to prevent cancer from developing. One study, for instance, is testing the effect of beta-carotene and retinol for asbestos workers who are at high risk for lung cancer. Another study is evaluating the role of dietary fiber combined with calcium in individuals who have a high risk of colon cancer.

During the last decade, a number of studies have shown that the cooking of meat, under certain circumstances, produces mutagens which may contribute to a person's risk for cancer of the stomach, large intestine, or other organs. Of these mutagens, the most important are a group referred to as heterocyclic amines. They are important as they are formed at ordinary relatively low household cooking temperatures by grilling, frying and broiling meats. A number of heterocyclic amines are formed in cooked ground beef, a major protein source in the American diet. Studies of carcinogenesis, metabolic activation, clearance from the body and effects on DNA are underway in animals which will eventually lead to estimates of their risk.

Recently, NCI-supported scientists have made a number of important genetic discoveries. Among these: the location of abnormalities on chromosome 17 believed to contribute to the suppression of lung cancer, colon cancer and breast cancer (damage at this site results in a loss of protection against cancer); the location of the gene responsible for familial malignant melanoma on chromosome 1. (Familial melanoma comprises about 10 percent of all cases of malignant melanoma); identification of five proteins produced by various genes implicated in the process of metastasis (the wild spread of cancer). Researchers at the NCI-Navy Oncology Branch have identified specific chromosomal deletions in various tumors, including lung cancer, which suggest that anti-oncogenes, also called tumor suppressor genes, are important in the development of these malignancies. These discoveries pave the way for new treatments to prevent or inhibit metastasis.

In a direct approach to reducing cancer death rates, the NCI makes state-of-the-art information about cancer available through a national information system established in 1976. Anyone in the United States can reach the Cancer Information Service (CIS) at its toll-free 1-800-4-CANCER number. CIS also has access to NCI's Physicians Data Query (PDQ), a computerized system, which lists state-of-the-art treatment and clinical trials throughout the United States, Canada and Europe.

NCI tracks cancer incidence and mortality rates through a variety of means. The main tool is the Surveillance, Epidemiology and End Results Program (SEER). This tumor registry system was established in 1973 and is structured to accurately represent a sampling of the total population. SEER is being expanded to include more extensive samples of minority and rural groups. For rural Americans, crucial information as to the relationship between occupational risks, including factors such as exposure to pesticides will be generated. For example, studies have shown that while overall mortality among farmers is generally lower than that of the national average, they may have an increased incidence and higher death rates from certain cancers. Furthermore, epidemiologic studies of farmers and others who use pesticides show an slightly elevated risk of cancer with exposure to these chemicals.

NCI is expanding its information base on cancer in Hispanic communities with an eye to identifying more precise needs of cancer control, developing intervention studies and studying cultural barriers to cancer control and prevention goals.

Formal organizational networks for Blacks and Native Hawaiians have helped to develop a cadre of researchers with sensitivity to cancer control needs of these communities. The National Cancer Control Research Network for Blacks is an excellent source of information dissemination on a series of important cancer prevention and control research issues. In addition, in support of Native American issues, NCI has funded two Interagency Agreements with the Indian Health Service; one for a five year Alaska Cancer Surveillance Initiative to provide baseline cancer incidence and survival information and a second to perform a risk evaluation for Native American groups in the continental United States.

Information alone is not enough to convince people to make lifestyle changes. More than 25 years after the Surgeon General published his landmark report on smoking, 50 million people still smoke. Furthermore, there are 3,000 new smokers in the U.S. each day; and sadly, adolescents are still tempted to smoke. To meet this challenge, NCI has developed several large smoking reduction research programs. One is the American Stop Smoking Intervention Study, or ASSIST/2000. This program, conducted with the American

Cancer Society will reach over one-fifth of the U.S. population and at least 15 million smokers. Another is the Community Intervention Trial for Smoking Cessation (COMMIT) which began in 1986. COMMIT involves more than two million people in the United States and Canada. It is aimed at heavy smokers, those who smoke 25 or more cigarettes a day.

NCI began a National Breast Screening Awareness Campaign using mass media materials, physician and patient education to increase the use of mammography. Last Fall, a Women's Leadership Summit on Mammography was held on Capitol Hill to launch this campaign. Where early detection programs or state-of-the-art treatment programs have been established, beneficial results are already being seen. A report from the San Francisco/Oakland based SEER cites "striking changes in diagnosis and treatment of breast cancer," a decrease in mortality from 1970 to 1986 from breast cancer due to detection of early lesions and a dramatic shift towards less radical surgical treatment.

There have also been advances in treatment of breast cancer including where appropriate, lumpectomy instead of mastectomy, and improved breast reconstruction. In addition, now there are new tests derived from molecular biology capable of identifying those women would benefit from additional therapy after surgery.

In addition to lifestyle changes, chemoprevention, or the adding of micronutrients or vitamins to the diet, can prevent cancer in some populations. Studies are being carried out in breast, lung, colon, bladder, and skin cancers with agents related to the retinoids, beta-carotene, vitamin E, selenium, and other substances. Currently 19 agents are undergoing clinical testing, 250 agents are in preclinical investigations and some 800 are being reviewed. These include large international studies testing chemoprevention in countries with high rates of specific cancers, for example, a lung cancer study in Finland involving 29,000 people and an esophageal cancer study in China involving 34,000 people.

Drug development is conducted in an expedited manner with the result that new anti-cancer and AIDS drugs have recently reached clinical use. For example, New Drug Approval status has been given to ifosfamide, flutamide, carboplatin, and fludarabine for treatment of metastatic stage of testicular, prostatic, and ovarian cancer and for chronic lymphatic leukemia (CLL), respectively. Fludarabine phosphate represents a significant advance for the treatment of CLL, the most common kind of leukemia in adults, with about 9,600 new cases diagnosed each year. To date, most patients become refractory to standard treatment and die within two to three years.

In the 1970s, NCI worked with FDA to develop a very valuable interim FDA classification: the Group C category. This has been the model for the FDA Treatment Investigational New Drug (Treatment IND) category. The Group C category makes new and effective drugs available to physicians prior to full FDA approval for treatment of appropriate patients who are ineligible for NCI clinical trials. This is extremely important as often experimental drugs are the only effective treatment available. NCI placed a number of drugs in the Group C category last year: levamisole plus 5-fluorouracil for adjuvant treatment of Dukes' C colon cancers; deoxycoformycin for the treatment of hairy cell leukemia refractory to the standard treatment of alpha interferon; and fludarabine phosphate for refractory chronic lymphocytic leukemia (CLL).

Recent research at the NCI-funded Cancer Center at the University of Arizona demonstrated that adding the drug verapamil, a calcium channel blocker used in cardiology, to the usual chemotherapy regimen reduced the drug resistance that had occurred in patients with refractory myeloma and non-Hodgkin's lymphoma. There was a notable treatment benefit in using this approach in refractory patients.

Many cancer centers credit the NCI-core grants with their ability to attract and hold top flight staff. The Director of the Center for Cancer Research at the Massachusetts Institute of Technology cites the recruitment of Dr. Susumu Tonegawa to the center where he received a Nobel Prize to continue his studies, on the immune system. Other centers, such as the Norris Cotton Cancer Center in Hanover, New Hampshire, offer most of the state-of-the-art cancer care for large numbers of rural poor in their region.

Metastasis, the spread of cancer from the original tumor to other parts of the body, is the major cause of cancer treatment failure. NCI investigators have identified and characterized a set of gene products which may play a role in the regulation of tumor invasion and metastasis. These gene products include: laminin receptor, autocrine motility factor, NM23 metastasis suppressor protein, type IV collagenase, and TIMP-2 metalloproteinase inhibitor. There has been a need not only to understand the steps in this process, but also to predict which tumors are likely to metastasize, to identify microscopic hidden tumors, to eradicate metastatic colonies and to treat cancer that has invaded adjacent tissues. This new understanding of these gene products will lead to solutions to these problems.

Angiogenesis, the forming of new blood vessels, is a critical and limiting step in tumor progression. Understanding this process is crucial for determining the steps involved in tumor development or suppression. New studies on transgenic mice which develop tumors of the pancreatic islets have demonstrated that the initiation of angiogenesis is an independent event occurring only in certain cells which become malignant by the activation of some positive switch.

• Genetic studies have traced the progression from benign adenomatous polyps to colorectal tumors thus identifying such polyps as a precursor to the carcinomas. Earlier work had shown that mutations in the ras oncogene were present in a high percentage of colorectal tumors. It has now been demonstrated that these alterations are very early events which can also be detected in benign lesions and perhaps even in nearby areas of the lining of the colon. Further analysis has shown that there are other important chromosomal alterations which occur in these growths that are associated with more aggressive disease. Correlations are being sought between specific chromosomal alterations or changes in the regulation of certain genes in the regions of these alterations and the behavior of the tumors.

Genetic studies are improving the ability of clinicians to predict which early stage breast cancer patients are likely to respond completely to initial treatment and which will require additional therapy. A number of indicators are used, including lymph node involvement, the amount of DNA in the cells (ploidy), and the presence or absence of estrogen and progesterone receptors on cells. The presence of additional copies of an oncogene HER-2/neu and indications of levels of the epidermal growth factor receptor may allow selected breast cancers with a high probability of recurrence to be distinguished from those breast cancers unlikely to recur.

Monoclonal antibodies to circulating breast epithelial cell antigens have shown potential for predicting clinical course, response to therapy and recurrence in patients with breast cancer. During the past year, several groups have cloned and sequenced genes for these proteins and have determined protein sequences which suggest that several potentially useful monoclonal antibodies react with different portions of the same protein. Knowledge of this sequence will allow the generation of synthetic antigens that may result in specific new monoclonal antibodies that are better able to detect the protein and thereby improve prediction of the clinical course of breast disease.

A consistent loss of a specific region of the short arm of chromosome 3 is associated with an inherited form of renal cell (kidney) cancer, as well as with the sporadic form of this disease. Deletions in the same region of this chromosome have also been implicated in small cell carcinoma of the lung. An intense effort is underway to "map" chromosome 3 to determine the exact location of the gene or genes associated with these tumors.

Clinical trials are studying strategies for combining or administering treatments to make them more effective and to reduce the possibility that the patient will become resistant to the drug or suffer adverse effects from the treatment.

Genetically engineered treatments are being developed in the laboratory which use monoclonal antibodies capable of seeking out specific tumors combined with potent plant or bacterial toxins that penetrate and kill cancer cells. To circumvent the problem of the human immunologic response to mouse antibodies, hybrid molecules have now been produced by recombinant DNA techniques which allow the production of molecules containing the mouse antitumor segments coupled with a carrier backbone specified by the human gene sequences.

High priority trials on the treatment of breast cancer are comparing the effectiveness of drug tamoxifen, with and without radiation therapy. Studies have shown that tamoxifen with radiation therapy has helped to prevent breast cancer from recurring in women whose cancer has not spread to nearby underarm lymph nodes. Another study examines two combinations of adjuvant chemotherapy followed by a comparison of tamoxifen or no future treatment, for node-negative patients. Over 2,600 women will participate, but nearly 70,000 women have similar cancers.

Two new drugs are in clinical trials: suramin against prostate and adrenal cancer and amonifide against breast cancer. The clinical activity of other new drugs (taxol in ovarian cancer, fludarabine in chronic lymphocytic leukemia, carboplatin in head and neck cancer and other cancers) has been confirmed. Bone marrow colony stimulating factors have proved effective in hastening the recovery of normal bone marrow during high dose chemotherapy, and radioisotope-labeled monoclonal antibodies which recognize lymphoma tumor cells have produced striking antitumor responses in mycosis fungoides, a type of lymphoma involving the skin, when used in combination with interferon. The use of interferon with 5-fluorouracil has also produced greater than expected response rates in advanced colon cancer.

The University of Arizona Cancer Center, recognizing their state as having among the highest rate of malignant melanoma, a deadly skin cancer, has targeted this cancer for a broad range of research ranging from studies of chromosomal abnormalities to studies of various sorts of radiation, including sunshine as "initiators" of relevant permanent genetic changes. Several chemoprevention studies are underway with Arizona residents, testing the use of Vitamin A derivatives (retinoids) and selenium to prevent cancer.

Radiotherapy has been undergoing change. Neutron therapy, a non-conventional form of heavy particle radiation not dependent upon oxygen for cell killing, now appears to be the treatment of choice for parotid gland tumors and also has decreased the recurrence rate for prostate cancer. Clinical trials in lung and head and neck cancer using this methodology are continuing at three NCI-supported facilities. Proton beam therapy, using another unconventional heavy particle, is being explored for a variety of cancers.

In an effort to improve conventional therapy, drugs that sensitize tumors to the effects of radiation have been developed. A new agent, SR2608, has entered clinical trial and will be the subject of expanded trials in the Radiation Therapy Cooperative Group.

Experimentation with alternatives to the traditional once daily use of radiation therapy has led to markedly improved survival rates (greater than 50 percent disease-free survival at two years) for patients with small cell lung carcinoma who received twice daily radiation treatments in combination with chemotherapy. This regimen will be used in new studies to evaluate the response of other tumors to radiation therapy. Thus there is a rapidly expanding array of potential therapies for clinical trial research.

Basic research funded by the NCI illuminates fundamental human biology, which many times has dramatic implications for diseases other than cancer. Researchers in Utah and at the NCI Frederick Cancer Research Facility discovered that an oncogene met is located close to the gene for cystic fibrosis. This discovery provided scientists with a marker which greatly facilitated the recent discovery and cloning of the gene for cystic fibrosis.

Recently the gene for the more common form of neurofibromatosis (NF-1) was localized on chromosome 17, and the less common form, NF-2, on chromosome 22. A multifaced clinical study of both forms of NF is being conducted by NCI scientists with other investigators. Results thus far show that the gene action produces much greater impairment within the nervous system than was known previously. Imaging of the brain by nuclear magnetic resonance provides early detection of acoustic neuromas in NF-2 and permits prompt removal. There is no cure yet for the neurofibromatoses, but these genetic studies offer promise of early detection and less extensive corrective surgery.

The development of transgenic mice has rapidly advanced the ability of researchers to study cancer. First developed in 1980, the procedure was evolved that introduces genes into the germline of mice by microinjecting appropriate DNA fragments. About 25 percent of the mice that develop from this procedure retain the foreign DNA in all of their cells and transmit it to half of their offspring. This allows study of specific gene expression and the potential of such genes to cause malignancy. Thousands of genes can now be introduced, allowing for important studies of issues of sequential triggering and expression of mammalian development and examination of misregulation -- critical to carcinogenesis. Transgenic technology has provided advances in many areas of cancer research including immunology, drug resistance, cancer etiology and the biology of gene expression and regulation.

The papillomaviruses are small DNA-containing viruses which usually cause benign skin growths or lesions, such as warts or papillomas in animals and man. Human papillomaviruses have now been linked to human cervical carcinoma and other related cancers including carcinomas of the penis, vulva and anus. There are approximately 500,000 deaths a year throughout the world from cervical carcinoma, 6,000 in the United States.

A new atlas of geographic patterns of cancer mortality, for a variety of cancer sites over three decades, among non-whites will be published in 1990. The maps highlight geographic areas having unusual variations and trends in cancer risks among non-white and provide etiologic leads -- such as regional or occupational patterns -- that can be evaluated by more definitive epidemiologic studies. There is a tendency toward more uniformity of rates, however there is a notable concentration of prostate cancer among Blacks in the southeastern part of the country, with clusters of high-rate areas emerging recently in the Carolinas.

NCI epidemiologists have found that alcohol combined with tobacco smoking contributes to cancers of the oral cavity, pharynx, esophagus, and larynx among American men and women. A high intake of both cigarettes and alcoholic beverages resulted in a greater than 35-fold increase in the risk of oral and pharyngeal cancers. This study also showed that, even among non-smokers, the risk of these cancers rose with increasing alcohol consumption, suggesting that alcohol itself is carcinogenic in humans. In a study in coastal South Carolina, the high intake of moonshine whiskey was implicated in the longstanding elevation of esophageal cancer rates among Black American males living in the area.

NCI has developed materials to help health professionals educate the public about the importance of eating a diet high in fiber and low in fat: "Eat Your Way to Good Health" -- a nutrition kit designed for Black communities; "Eating for Life" -- a booklet created in collaboration with the National Heart, Lung, and Blood Institute and being promoted by three private sector companies and a supermarket trade association; "Eat for health" -- a successful supermarket education program is now being extended to another supermarket chain with minority customers.

NCI is working in a number of areas to assist the District of Columbia Health Department and various other groups to address the high rates of cancer mortality in the District. One project, a special communications initiative was developed to assist the District Health Department in developing and implementing an effective cancer prevention and control plan for the city. Anti-smoking public service announcements featuring the Washington Bullets basketball coach were done and the message approaches developed in the District of Columbia will be applied to Black communities throughout the Nation.

Technology transfer of research results from basic studies in the laboratory to the clinical site takes place in some cases through cooperative research and development agreements (CRADAs) with private industry. This process requires expert skills in patent law and careful coordination with NIH, PHS, and DHHS policy. In 1989, NCI executed 19 CRADAs and has 40 more under negotiation. In addition, NCI submitted 56 employee inventions to the Patent Branch, DHHS and processed 125 material transfer agreements.

The NCI collaborations in cancer research cross many boundaries. Currently, NCI has signed Memoranda of Understanding with cancer institutes or organizations in China, Egypt, Federal Republic of Germany, France, Hungary, Italy, Japan, Korea, Poland, and the Soviet Union. In addition, NCI participates in NIH-signed international agreements with 29 other nations. These bilateral agreements are administered through the Office of International Activities (OIA) and specify exchanges of scientists for collaborative cancer research. The OIA also administers grants, contracts, cooperative agreements, and fellowship programs with international organizations and laboratories.

Cancer training programs are the future of the NCI. The research manpower development programs are aimed at recruiting and training research scientists, clinical researchers and educators who will provide a strong base for the continued progress of cancer research in the next several decades. NCI's training programs, in effect, also provide a crucial labor pool for the biotechnology and pharmaceutical companies of this country.

The NCI is committed to the recruitment and training of minorities in the sciences and has intensified its efforts in this regard. During the past year, the requirements for an institutional grant award were changed and now all applications must include a plan for the recruitment and training of minority investigators. In addition, special emphasis was placed on recruitment of young minority students into the cancer education program. This program has awarded grants for training doctoral-level candidates in cancer prevention and control; others award support for high school, college, medical, dental, nursing, and public health students to work in cancer research laboratories during their non-school time.

AIDS Research Program

Fiscal year 1991 will mark NCI's tenth year as a major contributor to our country's efforts to fight AIDS. During the past decade, NCI has established a comprehensive Preclinical AIDS Drug Screening Program now capable of testing well over 10,000 new compounds per year for activity against the human immunodeficiency virus (HIV). From this program has come AZT, the only agent proven to prolong the lives of AIDS patients and dideoxyinosine (ddI), another new drug with promising anti-retroviral activity, recently approved by the FDA for Treatment IND use in patients with AIDS who are intolerant to AZT. In addition, NCI has established a special AIDS Vaccine Task Force which is committed to pursuing a coordinated, multi-pronged approach to the development of an effective AIDS vaccine. In the past decade, NCI has also built major programs investigating the pathogenesis of AIDS, the biologic mechanisms by which the HIV causes infection, immune system destruction, multi-organ system dysfunction and some specific HIV-related cancers. Lastly, NCI has undertaken several epidemiologic and natural history studies, both descriptive and interventional, in the United States and in many countries abroad. These studies aim to determine the time course of HIV infection and of overt disease, to identify the major risk factors for acquiring HIV, and to design strategies to interrupt these processes.

Recent Research Accomplishments

The expression of HIV in infected human cells is greatly increased through the action of two essential HIV regulatory proteins, *tat* and *rev*. The action of the *tat* protein is to increase the transcription of HIV genes; *rev* promotes the transport of HIV mRNA from the nucleus to the cytoplasm and increases the half-life of the HIV mRNAs. Since last year, work has progressed in synthesizing large enough quantities of the *tat* and *rev* proteins to study the precise mechanisms of HIV gene regulation. *In vitro* systems are being developed to study transactivation, to characterize the structure of these molecules and to quickly and specifically detect their presence in human cells. This year, several new HIV mRNAs have been identified in infected human cells using Polymerase Chain Reaction (PCR). These mRNAs have been cloned and sequenced and their ability to be translated into important functional proteins is being investigated.

This year NCI scientists have generated transgenic mice which express the *tax* protein, one of the regulatory proteins of HTLV-I and HTLV-II which controls virus production. Animals expressing the *tax* protein have been found to develop Schwann cell tumors, tumors of the sheaths surrounding nerves, with high frequency. NCI scientists have determined that the *fos* oncogene is selectively activated in some of the tissues of these *tax* transgenic mice suggesting that the *fos* oncogene and the *tax* protein may play a role in tumorigenesis in these animals. These results may shed light on the mechanisms by which human leukemias develop in association with HTLV-1 infection.

Vigorous efforts are underway to elucidate the structure and function of the HIV integrase protein (IN) which promotes the integration of the HIV provirus into normal human DNA thereby establishing infection. NCI scientists have successfully expressed the integrase protein in *E. coli* bacteria and have begun efforts to purify the protein and to prepare antibodies against it. Work is underway to develop an *in vitro* assay system to analyze the biologic activity of the *E. coli*-made integrase.

Critical studies are being pursued to elucidate the nature of the immune dysregulation that occurs prior to the development of symptomatic AIDS. During the past year, three distinct categories of T-helper cell immune dysfunction have been identified in asymptomatic HIV-infected individuals. These categories of T-cell dysfunction are first, loss of the immune response to infectious agents such as viruses; second, loss of the immune response to foreign transplantation antigens such as skin grafts; and third, loss of responsiveness to mitogens -- agents which induce normal T cells to divide. Recent studies have shown that there is a sequential progression from one category to the next that is predictive for progression towards AIDS, and that this immune dysfunction can be detected up to two years before any other signs of AIDS are observed. Current studies suggest that the mechanism responsible for this early immune dysfunction may be due to the production of a type of "autoantibody" that blocks the interaction of the helper T cells with other cells of the immune system (called antigen presenting cells-APC) that are required for helper T cell activation. Ongoing studies suggest that some AIDS patients (but not asymptomatic HIV-infected individuals) have one or more defects in antigen presenting cell function. Thus, even if T-helper cell defects could be corrected in AIDS patients, a second defect in antigen presenting cells would prevent the immune system of such patients from functioning normally. Understanding the mechanism responsible for the immunosuppression associated with AIDS is important to our understanding of the pathogenesis of this disease.

Exciting preliminary results about the production of lymphokines -- factors which regulate the cellular components of the immune system -- by HIV-infected cells will provide the fundamental underpinnings for the development of therapies to boost immune function in AIDS patients. NCI scientists have found that lymphokines produced by HIV-infected cells may be important regulators of HIV production by human monocytes. The DNA segments which code for two novel lymphokines, neutrophil and lymphocyte chemotactic factor (Interleukin-8) and monocyte chemotactic and activating factor (MCAF) have been isolated. It has been found that IL-8 increases the ability of human neutrophils to kill certain funguses; this substance may therefore be useful in treating AIDS-associated fungal infections.

NCI's epidemiology program, through national and international studies on various subpopulations with AIDS or seropositive for HIV-1 infection, has made significant contributions to understanding the natural history, transmission, and pathogenesis of this disease. Populations under study include hemophiliacs and their families, infected women and their infants, and AIDS patients with cancer. International AIDS studies are being performed in the Mediterranean, Africa, the Caribbean and in South America.

Results have recently been published by NCI investigators of the largest study of HIV infection in hemophiliacs to date. By testing previously frozen serum samples for HIV antibodies, this cohort is the world's largest with documented incident HIV infections. It includes 1,219 registered hemophiliacs from 14 medical centers nationwide, 55 percent of whom were HIV-positive, who participated in the study. The annual incidence of developing AIDS ranged from zero during the first year after seroconversion to seven percent during the eighth year. One very important finding of this study was that the risk of developing AIDS is directly related to age in the hemophiliac population with adults developing the disease sooner after HIV infection than adolescents or children. At eight years after seroconversion, scientists found the lowest cumulative rate of AIDS development in the group ages one to 17 years (13.3 percent). Among those ages 18 to 34, the rate was 26.8 percent, while those ages 35 to 70 had the highest rate of AIDS development, 43.7 percent.

Another important finding of this study was the demonstration that the HIV epidemic appeared in hemophiliacs in late 1978, spread rapidly during the early 1980s, and ended by 1986 due to the wide-spread screening of the blood supply. Subjects with severe hemophilia A became infected earlier and at a much higher rate, eventually 77 percent, than those with other clotting disorders. Potential co-factors, such as race, type and severity of hemophilia, and dose of clotting-factor concentrate did not affect AIDS incidence among HIV-infected hemophiliacs. A number of laboratory markers have identified seropositive individuals at highest risk of developing AIDS, particularly those with low CD4-cell counts, p24 antigenemia, lack of anti-p24, and circulating interferon.

In collaboration with the National Institute on Drug Abuse, 1,766 parenteral drug users recruited from treatment programs from across the U.S. were evaluated for prevalence of HIV and/or HTLV-I/II. Three-hundred seventy (21 percent) had HIV antibodies, with substantially higher rates among blacks (33 percent) and Hispanics (20 percent) than whites (10 percent). HTLV-I/II antibodies were noted in 189 (11 percent) of the subjects, including 19 percent among blacks, 8.5 percent among Hispanics, and five percent among whites. HTLV prevalence increased with older age in all racial groups but was similar in males and females.

Two new analyses have been completed on the cohorts of homosexual men that NCI has been following since 1982. First, two potential serological markers of progression to AIDS, neopterin and beta-2-microglobulin, have been compared to CD4 counts. Presence of neopterin is clearly an independent AIDS marker, indicating a high AIDS risk some three years before diagnosis. The value of beta-2-microglobulin as a marker is clear in the year before AIDS diagnosis.

In a second analysis, sexual activities were evaluated with respect to knowledge of one's own and one's partners' HIV status. Results indicated that risky homosexual activity has fallen markedly since 1982, but that one-third of men continued to engage in receptive anal intercourse, most without a condom or with partners of unknown HIV status. On the positive side, the findings also indicated that men almost never knowingly had sex with a partner of opposite (i.e., discordant) HIV status. A third analysis of neuropsychological abnormalities by HIV immunodeficiency status is in progress.

Another study is being conducted in close collaboration with the National Institute of Child Health and Human Development, the State University of New York Health Sciences Center at Brooklyn, and the Albert Einstein College of Medicine in the Bronx, New York. Two-hundred fifty women have been enrolled during pregnancy, approximately 40 percent of whom are HIV-infected, and they have given birth to approximately 150 babies. Thus far, HIV-infected women with advanced immunodeficiency have developed Pneumocystis pneumonia and other opportunistic infections at a high rate, but there have been no marked increases in adverse pregnancy outcomes. Early evaluation and follow-up of the children suggest that newborns of HIV-positive women are very like those of HIV-negative women, although growth in weight, length, and head circumference may be very slightly delayed. No clear HIV-related neurological syndrome could be defined in the first year of life, but neuropsychological evaluation has suggested that both verbal and motor development may be significantly delayed in HIV-infected infants.

Spouses and long-term heterosexual partners of patients in various clinical stages of HIV infection are being followed in order to obtain a better understanding of risk factors for acquiring HIV and of disease progression. Among the spouses (partners) enrolled, there was no difference between men and women in the seroprevalence of antibodies to HIV (26 percent and 21 percent respectively). Presence of HIV antibody in a spouse correlates directly with the severity of HIV disease in the index case, the presence of p24 antigen in the index case, a low CD4 cell count in asymptomatic index cases, presence of genital herpes or gonorrhea in the spouse, and with lack of condom use in the preceding year. The length or frequency of sexual contact and the types of sexual activity did not correlate with the presence of antibody to HIV in a spouse. In this population, the risk for heterosexual acquisition of HIV appears to be relatively equal for men and women in a monogamous relationship, and increases with advancing disease and the development of p24 antigenemia in the index case. In addition, other sexually transmitted diseases or potential breaks in epithelial membranes may play a role in heterosexual transmission of HIV. Children of the index cases have also been enrolled in the prospective study. All children seropositive to HIV were born to mothers with HIV infection; none of the seronegative children have converted during the study period. Despite close contact among family members, there is no evidence of spread of HIV within households.

An international registry of AIDS victims has been established for persons with documented dates of HIV seroconversion in order to evaluate co-factors and trends of AIDS risk. Thirty-eight investigators from three continents have contributed 1,115 subjects for analysis. Analysis has focused on the 816 subjects enrolled in prospective studies who had HIV seroconversion documented within a window of 25 months. Within risk groups, time-to-AIDS was the same in all geographic areas and among early (pre-1985) and later seroconverters. Children with hemophilia progressed to AIDS more quickly than did adults, and homosexual men progressed to AIDS more quickly than did adult hemophiliacs because of an excess of Kaposi's sarcoma in the former. Time-to-Pneumocystis pneumonia was similar in hemophilic and homosexual adults. Thus far, too few drug users, heterosexual partners, and transfusion recipients have been enrolled to make evaluation possible, but follow-up is continuing and additional contributions are being sought.

Since mid-1987, the national AIDS incidence figures have fallen below previous projections in certain risk groups. NCI scientists have recently provided preliminary evidence which shows that effective medical care is having an impact on AIDS rates nationally. A report of this data will be published early this spring. Azidothymidine (AZT) was approved by FDA in

March, 1987 for the treatment of patients with AIDS and AIDS-related complex (ARC). Ongoing reviews of treatment patterns suggest that possibly half the AZT administered in 1987 was given to patients with ARC, thereby delaying or preventing the diagnosis of AIDS. Other treatments to prevent Pneumocystis carinii pneumonia (thereby delaying an AIDS diagnosis) in patients with ARC were also under investigation in 1987. NCI scientists have calculated that treatment of only a few thousand ARC patients with AZT could account for the observed "AIDS deficits" in national rates.

The "AIDS deficit" began in mid-1987 for several of risk groups; these deficits are greatest in groups expected to have the best access to medical care. For example, white homosexual and bisexual men had a deficit of 25 percent in the last half of 1988, compared to 14 percent for blacks. White homosexuals in non-urban centers had a deficit of 16 percent, whereas white homosexuals in New York City, Los Angeles and San Francisco, where medical experience in treating AIDS is greater, had a deficit of 38 percent. Deficits have been seen among homosexual and bisexual men, homosexual intravenous drug users, hemophiliacs and transfusion recipients. The deficits increased over time from mid 1987 through the end of 1988, as one would expect as increasing numbers of patients began treatment. No deficits were found in 1987 for non-homosexual intravenous drug users, heterosexuals or Haitian immigrants, and only very small deficits were noted by the end of 1988 in these groups. One might expect these three groups to be less likely to obtain effective medical care, either because they are unsuspecting of AIDS risk or for economic reasons.

HIV-infected individuals are also at risk for the development of a variety of cancers in addition to Kaposi's sarcoma such as Hodgkin's disease, non-Hodgkin's lymphomas, anal squamous carcinomas and T cell chronic lymphocytic leukemias. The numbers and types of such AIDS-associated malignancies are increasing rapidly; in one recent study, nearly 15 percent of individuals from a group of 200 AIDS patients developed a variety of neoplastic sequelae.

NCI has developed a comprehensive program for the discovery and development of drugs with anti-HIV activity. This program includes three basic components: 1) a high capacity drug screen to assess compounds for activity against the AIDS (HIV) virus; 2) a laboratory-based effort for developing novel approaches to drug treatment and; 3) a program for the preclinical and early clinical development of drugs with promising anti-HIV activity. This program is a unique resource because of its comprehensive approach to AIDS drug development. It has been responsible for discovering and developing many of the investigational drugs available for the treatment of AIDS. For example, azidothymidine (AZT), the only drug approved and marketed for the treatment of HIV infection, was discovered and partially developed through this program. Dideoxyinosine (ddI) was also developed through this program and has been recently granted Treatment IND status for use in AIDS patients who cannot benefit from treatment with AZT. Additionally, NCI has a number of promising new compounds under clinical development, including dideoxycytidine (ddC) and the fluorinated versions of ddI and ddC. To a lesser extent, the NCI has been involved with the discovery and development of agents for opportunistic infections, including trimetrexate for the treatment of pneumocystis carinii pneumonia (PCP).

A unique resource at NCI is the Preclinical AIDS Drug Screen. This was specifically developed as a rapid and high capacity screen for the evaluation of compounds submitted from any source, including the private sector and academic institutions. Since its implementation in 1987, over 27,000 screening tests have been performed with a current capacity of 900 tests per week. To date, over 7,000 unique chemical structures have been tested, of which 70 (one percent of all drugs screened) have been identified as having definite anti-HIV activity. At the current screening capacity, it is projected that up to 100 unique compounds with anti-HIV activity may be identified each year. Although on the surface this sounds like a large number, it is important to recognize that only a few of these compounds will be clinically useful. This is because after a compound is further evaluated for efficacy, pharmacology and toxic effects, it may be found not suited for full-scale clinical development. Decisions to proceed with further preclinical and clinical development are made at multiple steps along this developmental pathway by NCI's Decision Network, a committee comprised of NCI and NIAID scientists and clinical investigators. These decisions are crucial to ensure that the most promising new agents receive highest priority. With the currently available preclinical and clinical drug development resources at NCI, three to four compounds can be developed each year. Of course, as the preclinical drug screen identifies more than three to four high priority compounds per year, NCI will need to license these agents earlier in development to the private sector. It is important to emphasize that in the near future, the limiting factor for AIDS drug development will be the resources available for preclinical and clinical drug development and not the identification of active compounds in the AIDS Drug Screen.

In the past year, 16 compounds have been reviewed and approved by the Decision Network for further preclinical drug development. One of the most exciting aspects of these compounds is that many of them have unique structures and probably inhibit HIV through different mechanisms. This is critically important because experience in other diseases tells us that AIDS may be more effectively treated with drug combinations which block different points of the virus' life-cycle. Last year, some of the exciting compounds under development were discussed, including castanospermine, an inhibitor of the synthesis of functional HIV proteins, and carbovir, a nucleoside which, like AZT, inhibits HIV reverse transcriptase, thereby blocking conversion of viral RNA to DNA and its subsequent integration into the genetic material of the CD4 cell. In the past year, a number of new compounds or chemical classes have been identified. One such chemical class is a natural product extracted and purified from cyanobacteria. Initially, anti-HIV activity was identified in an impure extract of these bacteria; the active compound was subsequently purified and its structure determined by NCI scientists. Other promising classes of compounds include the suramin analogs, sulfated polysaccharides, concanavalin A, and a whole array of other discrete compounds.

NCI's supercomputer continues to play an important role in the study of the HIV virus. Last year we reported that special software programs had been developed for the supercomputer enabling scientists to predict the structure of the HIV genome and to look for correlations between the presence or absence of certain structural features and their possible functional correlates. These initial studies yielded the surprising result that regions of the genome having high variability in their amino acid sequence are deficient in stable structure, suggesting that these regions might vary with each strain and might be particularly susceptible to mutation. This same kind of analysis has revealed three regions of stable structure that appear to correlate with the regulatory regions of the HIV genome.

Another recent accomplishment of the supercomputer has been the determination of the structure of the HIV protease molecule. The calculations for this project would have required over 30 days of time on a VAX computer but were accomplished in only 48 hours using the supercomputer.

NCI's intramural AIDS program conducts early clinical testing on promising anti-HIV drugs in adults and children. Over the past year the intramural program has tested a number of new drugs including several biologic response modifiers (BRMs). These molecules include the lymphokines which play important roles in orchestrating the immune response. These BRMs, if clinically active, would be potentially very useful in treating AIDS patients suffering from severe immunodeficiencies.

One of the most exciting new drugs to emerge from NCI's Preclinical Drug Screen is dideoxyinosine (ddI). During the past year, a Phase I study of ddI revealed that this drug has low toxicity in the short term and, unlike AZT, does not cause significant bone marrow toxicity. Results recently published demonstrate that ddI at the higher doses, like AZT, causes a rise in the number T4 cells and a significant decline in the p24 antigen level, the latter a marker for viral and disease activity. For these reasons, ddI will soon be compared to AZT in a larger study designed to further study its efficacy and longer term toxicity. The Food and Drug Administration has recently approved a Treatment IND for ddI to be used to treat adults with AIDS who cannot benefit from AZT therapy and who are not eligible for participation in a clinical trial.

A Phase I study of dideoxycytidine (ddC) was also completed at NCI this year. This drug had previously been shown to be exceedingly potent against HIV at relatively low doses in cell culture. The Phase I study revealed that ddC has a markedly different spectrum of toxicity from AZT causing comparatively little bone marrow suppression, but significant peripheral neuropathy. This nerve damage was found to be reduced or eliminated at lower drug doses or by introducing ddC-free rest periods into the higher-dose treatment regimen. This Phase I study also showed that ddC is well absorbed from the stomach and achieves good penetration into the brain where HIV is often harbored.

A third Phase I study alternated treatment with AZT and ddC in an attempt to prevent the peripheral neuropathy of ddC and the bone marrow suppression of AZT. This is the first study designed to test a regimen of two alternating nucleoside drugs with potent anti-HIV activity. Such designs have great appeal not only to reduce toxicity, but also to circumvent the development of AZT-resistant strains of HIV. Eighteen patients have been treated with this combination and preliminary data suggest that this approach does reduce the toxicity of the individual agents and confers significant clinical benefit on certain patients. However, further testing is required to determine whether this combination is superior to treatment with either agent alone.

NCI scientists are also studying the ability of the bone marrow stimulator granulocyte macrophage colony stimulating factor (GM-CSF) to reduce the bone marrow toxicity of AZT. In the past year, 10 patients have been treated and preliminary results indicate that the combination of AZT plus GM-CSF can be tolerated for more than 14 weeks and may be less toxic than AZT given alone.

In another study, recombinant soluble CD4 is being administered as a continuous intravenous infusion to patients with AIDS or AIDS-related complex (ARC). This year, 17 patients have been treated at increasingly higher doses, some for prolonged periods. So far little or no toxicity has been seen.

NCI has placed significant emphasis on the testing of anti-HIV drugs in pediatric patients. This is a very high priority because the number of pediatric HIV infections are increasing rapidly due to the problem of intravenous drug use in women of child-bearing age. NCI scientists recently completed a study of continuous-infusion AZT in children with symptomatic HIV infection. It was especially important to study the concentrations of AZT in the central nervous system because HIV causes a high incidence of brain dysfunction, including loss of normal brain development in very young children.

Dramatic improvements occurred in all 13 children who had significant brain dysfunction prior to treatment. Serial IQ measurements before therapy and after three and six months of treatment with AZT showed significant improvements in overall IQ score. Of note, six children without detectable evidence of brain dysfunction prior to AZT also showed improvements in their IQs from baseline, suggesting that such impairment may be among the earliest manifestations of HIV infection in children.

This study is the first demonstration that AZT is beneficial in children with symptomatic HIV infection and will be important in winning full FDA approval of AZT for the treatment of children with AIDS.

In another pediatric study, ddC and ddI are being tested in children with symptomatic HIV infection. The children treated with ddC showed decreases in their viral p24 antigen levels and increases in the number of CD4 lymphocytes. Additionally, three children who presented with brain dysfunction showed evidence of clinical improvement. Thus far, no peripheral neuropathy from treatment with ddC has been observed in these children. A Phase I trial of ddI is also underway in children with symptomatic HIV infection. To date, 40 children (21 placental, 11 transfusion-acquired, and eight hemophiliacs), aged eight months to 18 years (median age 5.8 years) have been enrolled. Preliminary results from this study show that ddI has significant anti-HIV activity with significant improvements in T4 cell counts, p24 antigen levels, lymphadenopathy and weight gain occurring in several children. In two patients, head CT and MRI scans documented improvement in cerebral atrophy.

During the past year, NCI scientists have begun studying the use of photodynamic therapy for AIDS-related Kaposi's sarcoma. Kaposi's sarcoma causes significant disfigurement of the skin and is frequently difficult to treat with currently available therapies. With photodynamic therapy, patients receive intravenous hematoporphyrin (HPD), a compound toxic to cells when activated by certain wavelengths of light. The Kaposi's sarcoma lesions are then exposed to the activating light which induces tumor regression only in the light-exposed areas. Five patients have been treated to date and promising anti-tumor responses have been observed. Should further study confirm these findings, photodynamic therapy will be an important contribution to the treatment of this tumor.

In summary, NCI's intramural AIDS clinical trials program has led to the development of AZT and ddI for adults and is conducting trials to support full FDA approval of AZT for children with AIDS. Additionally, clinical and laboratory studies indicate that ddC and ddI are promising new anti-HIV drugs for both children and adults. These drugs will soon be entering large-scale trials to determine whether they are as effective as AZT and possibly less toxic.

Rapid progress has been made studying the biology of HIV in cell culture experiments and a number of viral genes and their functional properties have been identified. However, the absence of an animal model of the human disease has made direct studies of vaccine development difficult. Fortunately, a number of related animal viruses exist which share many properties with HIV. Studies of these related viruses in their natural hosts may provide appropriate models for AIDS vaccine development and evaluation. Each model provides investigators with insights on particular aspects of HIV pathogenesis.

A new animal model for studies on HIV has recently been developed which may permit the in vivo study of the stages of HIV pathogenesis, including infection, virus replication, latency and disease progression. Homozygous severe combined immunodeficiency (SCID) mice, which are genetically immunodeficient due to a lack of functional T and B lymphocytes, are unable to mount an effective cellular or humoral (antibody) immune response to foreign antigens. These mice, when implanted with human lymphoid tissue, develop a competent immune system. The transplanted lymphoid tissues contain functional lymphocytes which are susceptible to HIV infection, thus allowing these mice to mimic human infections with the virus and to serve as a small animal model to study the interactions of HIV with the human lymphoid system.

The simian immunodeficiency virus (SIV) induces an AIDS-like disease in rhesus monkeys with clinical symptoms similar to those observed in the human disease. This virus-host system provides an excellent model to investigate alterations in cells of the immune system during disease progression. Soon after infection, a subset of activated T lymphocytes increases in numbers in the lymph nodes of SIV-infected monkeys with the lymphadenopathy syndrome. The same type of lymphocytes from SIV-infected rhesus monkeys can block SIV replication in a tissue culture system, indicating that these T lymphocytes may contribute to containing or suppressing the progression of simian-AIDS. This is an important observation, since it is the first indication of a specific T lymphocyte subset that is effective in suppressing replication of a lymphotropic lentivirus, suggesting a possible strategy for the treatment of AIDS.

Antigenic variants of HIV have recently been detected although their role in the pathogenesis of HIV has not yet been determined. The equine infectious anemia virus (EIAV) provides an appropriate animal model to investigate this biological process. EIAV produces a recurring infection in horses which is temporarily brought under control by immune responses from the infected animal. Mutations in EIAV lead to antigenic variants which escape the previously established host immune responses, resulting in recurrent infections. Recent research demonstrates that mutations occur in the viral envelope gene during replication, possibly similar to that seen in HIV infection. Thus, EIAV may provide a model to investigate the molecular mechanisms involved in HIV antigenic variation and immune selection of variants arising during the course of infection in the natural host.

T cell immunity is likely to be an important component of the immune defense against the AIDS virus, since helper T cells are necessary for the humoral (antibody) response and for the cell-mediated cytotoxic T cell response. Last year we reported that computer analysis of the genetic sequence of HIV had made it possible to predict the stretches of amino acids on the surface of the HIV envelope protein likely to elicit an immune T cell response. Several protein fragments have been produced, some of which were successfully used to immunize mice and to elicit T cells that reacted with the HIV envelope protein. A recent discovery has been the identification of the first antigenic site of the AIDS virus recognized by cytotoxic (killer) T cells. This cytotoxic T cell peptide and three HIV-derived peptides recognized by T helper cells have been tested in humans and found to be capable of eliciting an immune response in normal individuals subsequently immunized with a recombinant HIV protein. Asymptomatic HIV-infected individuals also developed an immune response from these peptides.

Assays have been recently developed to monitor the immune function of chimpanzees vaccinated with various purified components of the HIV-1 protein envelope. NCI scientists have succeeded in developing an assay to determine the magnitude and specific type of cytotoxic T cell response in the chimpanzees which result from immunization with various HIV components and from HIV infection. These cytotoxic T cell assays complement the humoral assays currently used to monitor the animals' antibody response to vaccination. These two types of assays are being used to determine which type of immune response -- humoral or cytotoxic -- is more effective in preventing HIV infection.

Collaborative studies involving an accidentally infected lab worker have revealed many important parallels between HIV-1 infection of the human and chimpanzee. Both behave in a serologically identical manner, making antibodies which recognize all the major viral antigens. Virus can be re-isolated from peripheral blood mononuclear cells. Neutralizing antibody develops more slowly and in lower titer in the human than the chimpanzee; however, it parallels its biologic behavior exactly. Analysis by serotyping has revealed the subsequent serial isolation of viruses which are increasingly resistant to antibody neutralization. Amino acid analysis has revealed that amino acid substitutions in a portion of the viral envelope important in eliciting neutralizing antibody accompanies this viral resistance. These findings suggest that HIV-1 behaves similarly in humans and chimpanzees and further support the need for continued studies with this animal model.

Research Plans

Research on the pathogenesis of HIV infection explores the mechanisms by which the human immunodeficiency virus, HIV-1, succeeds in actually causing the Acquired Immunodeficiency Syndrome. This research involves detailed analysis of the structure and function of all the viral genes, including the genes which regulate transcription -- that is, the conversion of the integrated viral DNA into RNA -- as well as the proteins encoded by these HIV-1 genes. Understanding the pathogenesis of AIDS also involves deciphering which elements of the immune system are adversely affected by the HIV infection so that specific therapeutic targeting can be developed to protect the elements at risk. HIV infection also causes damage to several other human organs including the colon, brain, and retina and appears to play a role as well in the genesis of certain malignancies in AIDS patients. NCI scientists are studying several aspects of HIV pathogenesis including the mechanisms of infection and viral production, the contribution of other oncogenic viruses in the development of AIDS, the development of the associated immune dysfunction, and the genesis of Kaposi's sarcoma and other malignancies associated with AIDS.

AIDS patients infected with HIV are also invariably infected with other agents such as oncogenic DNA viruses and other human retroviruses. Due to the long latency period of HIV, co-infection with other viruses may be responsible for the activation of HIV expression, immune activation and the progression of the disease. Activation of HIV in vitro by DNA viruses such as herpes simplex virus type 1, adenovirus, cytomegalovirus, human herpes virus 6 (HHV-6) and human retroviruses HTLV-I and HTLV-II has recently been reported. An understanding of the role of these viruses in activation of HIV expression and progression of AIDS may be useful in the development of treatment modalities for patients with acquired immunodeficiency.

Infection with CMV is extremely common in AIDS patients and leads to severe gastroenteritis, retinitis and pneumonitis. It appears that an early gene of CMV can activate the HIV-1 promoter leading to increased expression of HIV-1. Examination of brains of patients dying of AIDS indicates the presence of both HIV-1 and CMV in the same cell. This observation suggests an important co-factor role for CMV and other herpesviruses including HHV-6. It will be important to examine the mechanisms of HIV-1 activation by CMV and other herpesviruses in order to be able to develop treatment and prevention strategies for AIDS.

For the first time, NCI scientists have an almost complete list of the HIV mRNAs produced in infected human cells. Scientists are planning to express the regulatory tat and rev proteins in bacterial expression systems to develop in vitro systems for transactivation studies. Mutagenesis studies will be undertaken to determine the exact function of these regulatory molecules.

Knowledge of the structure and function of E. coli-made integrase will be essential in the development of drugs designed to inhibit the integration of the HIV provirus. Scientists will perform x-ray crystallographic analyses to help in the rational design of drugs to inhibit this critically important protein.

The effects of monocyte chemotactic and activating factor (MCAF) on HIV production by monocytes and on HIV infection of other human monocytes will continue to be studied intensively. It will be critically important to understand how macrophages are activated, as this cell appears to be a reservoir for HIV. Such studies will aid the understanding of how to overcome defects in macrophage function and how to control HIV viral production in these cells. The role of lymphokines produced by HIV infected cells in bringing about immune suppression will continue to be probed.

The latency period between initial infection with HIV and the development of antibodies has recently been an area of active research. The polymerase chain reaction (PCR) technique will be used to detect HIV provirus in lymphocytes obtained serially from seroconverters in the MACS cohort. Sera and PBL will be studied 18, 12, and six months prior to the first positive Western blot and at the time of seroconversion. Preliminary results of PCR amplification data show that all seroconverters were PCR positive at the time of seroconversion, and most were PCR positive six to 12 months before the first positive Western blot. Additional seroconverters are being evaluated.

Preliminary analyses indicate that HIV-infected women transmit the virus to approximately 30 to 40 percent of their offspring, with premature babies appearing to be at three-fold higher risk than full-term babies. Decreasing antibody titers are noted at about nine months of age, and may take as long as 16 to 18 months to completely clear. The identification of HIV infection in children may be through the reappearance of HIV antibodies, occurrence of new antibodies, presence of virus in culture, or development of symptoms consistent with HIV-related disease. Remarkably, mothers who did transmit HIV to full-term babies had very low or absent antibody reactivities to gp120, the HIV envelope glycoprotein. Further laboratory characterization of this observation is in progress.

Several important implications follow from the hypothesis that treatment is reducing the national AIDS incidence rates. First, treatment effects must be kept in mind while interpreting current AIDS incidence trends. Paradoxically, ignoring treatment effects can lead to serious underestimates of the numbers of persons previously infected and can lead to an over-optimistic view of future AIDS incidence. Second, the data suggest a need to provide better access to treatment for those subgroups not showing "AIDS deficits".

NCI scientists will explore this treatment hypothesis further in the coming year. Additional data will be sought on the extent, timing and types of previous therapy, and statistical models will be developed to incorporate the effects of therapy in projecting future AIDS incidence and health care needs. Research is also needed to quantitate the economic and public health benefits of reducing AIDS incidence by various treatment strategies.

At NCI, the viral etiology of AIDS-related malignancies is being actively investigated. Several mechanisms of viral induction of neoplasia are possible. The HIV-1 virus or one of its genes may induce neoplastic transformation directly. Alternatively, HIV or one of its genes may interact with one of several DNA viruses, such as cytomegalovirus, human herpesvirus 6, human papillomaviruses or hepatitis B virus, or with RNA viruses, such as HTLV-1. Most AIDS patients are latently infected with these viruses. These viral co-factors may alter the course of HIV pathogenesis and lead to the development of neoplasia. In addition, HIV-induced immunosuppression may result in a latent virus, such as Epstein-Barr virus (EBV) or other lymphotrophic viruses, causing B cell lymphomas directly. The role that these and other viruses might play in the induction of neoplasia is not known. Future research will explore the prevalence of HIV and other viral co-factors in AIDS-associated malignancies, study the molecular events leading to the initiation and progression of disease, and investigate the molecular interactions between viral and cellular genes involved in host cell growth regulation in order to elucidate the mechanisms involved.

NCI scientists continue to expand the Preclinical AIDS Drug Screen and to develop novel approaches to drug discovery. Strategies are being designed to find drugs which will interfere with HIV infection and production at each step in the HIV life-cycle. By then treating patients with a combination of drugs which inhibit HIV at different points in the virus' life-cycle, therapeutic synergy can hopefully be obtained and the problem of resistant strains of HIV hopefully averted.

An important aspect of the AIDS Drug Development Program is the development of novel approaches to inhibit HIV. Such approaches must rely heavily on an understanding of the life-cycle of HIV. Through work performed at NCI and elsewhere, an in depth understanding of the biological and biochemical events occurring during the life-cycle of HIV has been achieved. Specific steps in this life-cycle potentially amenable to disruption with drug therapy have been identified and include: 1) the initial binding of HIV to T4 cells, a step necessary for infection; 2) the inhibition of HIV reverse transcriptase; 3) the regulation of HIV genetic material (DNA) through the HIV tat (trans-activating gene) protein; 4) the inhibition of HIV RNA translation into protein; and 5) the processing of HIV proteins necessary for the production of new virus particles. In order to develop drugs which block these points in the HIV life-cycle, it is necessary to design specific detection systems for each point in the pathway. Such assays are referred to as mechanistic assays. The development of such mechanistic assays for use in screening compounds with potential anti-HIV activity has therefore been a prime focus of investigation over the past year in NCI's drug development program.

NCI's AIDS Drug Screen Program has become a major resource for the private and academic AIDS drug development sectors and will continue to expand in the coming year. Scientists will continue to design methods to screen new agents using mechanistically-oriented assays. This is a high priority area because identification of compounds with different mechanisms of action against HIV will probably be important for the eventual control of the disease in HIV-infected patients. Specific areas that are being targeted are the development of antisense phosphorothioate dideoxynucleosides and reverse sense nucleotides. Additionally, development of anti-growth factor drugs such as suramin and suramin analogs is an important priority. NCI will also continue to expand its efforts to identify effective anti-HIV drugs from natural products. The increased acquisition of unique natural products and an expansion of the capacity to extract and identify active compounds will be a high priority for the Preclinical AIDS Drug Screen in the coming year.

A new recombinant protein has been produced that combines that portion of the CD4 molecule that attaches to the HIV virus with a powerful bacterial toxin, pseudomonas exotoxin (PE). This protein, termed CD4-PE, can attach to and kill HIV-infected cells in culture. Current studies are in progress to test the effect of the CD4-PE recombinant protein on different types of normal and HIV-infected cells.

Of particular interest, is the very recent finding that a common anti-clotting drug (dipyramidole), widely used in the treatment of cardiovascular diseases, appears to significantly increase the ability of AZT to inhibit replication of the AIDS virus in in vitro experiments. These results suggest that combining this drug with AZT or with other dideoxynucleosides (such as dideoxycytidine, ddC) would significantly enhance their effectiveness without any apparent increase in toxicity.

NCI is developing a program for the collection and isolation of natural products for the discovery of new drugs with anti-HIV activity. The impetus for the program comes from experience with cancer drug development which has derived some of its most active drugs from natural products. As mentioned above, this project has recently produced a new class of compounds with anti-HIV activity from cyanobacteria. NCI considers this program a high priority because it is anticipated that natural products will be a rich source of important compounds with anti-HIV activity.

The planned upgrade of the supercomputer facilities will allow novel approaches to problems that are too large and complicated for the current machine such as the prediction of the structure of the entire AIDS virus genome. Information from these studies will help target the most critical and accessible sites of HIV and will help researchers design new drugs that interfere with HIV infection with pathogenesis more effectively.

NCI is currently exploring the use of lymphokines as potential AIDS therapies. Two novel approaches are being undertaken. First, efforts are underway to identify lymphokines called colony stimulating factors (CSFs) capable of replenishing the CD4 cells in HIV-infected patients. This is being attempted by screening lymphocyte extracts for the presence of growth stimulatory activity for precursor T cells. A large number of lymphokines have been screened including IL-1, IL-2, IL3, IL-4, IL-6 and gamma interferon. Animal models are also under development to assess promising lymphokines as therapies.

In the coming year, a high priority for NCI will be the continued development of new BRMs for the treatment of AIDS. Through genetic engineering, many of these proteins can now be manufactured in large quantities and clinically tested. In the coming year, scientists will continue to focus on the identification of new cytokines which stimulate the immune system. Clinical trials underway or planned for the coming year include the testing of IL-1, IL-3, IL-4, TGF-beta, glycosylated IL-2, and M-CSF. Each of these compounds has specific roles in activating and stimulating the immune system. Should an AIDS patient's immune system be improved by these cytokines, protection against opportunistic infections could be expected.

NCI is also developing compounds with potential efficacy in the treatment of AIDS-related tumors. One such compound, suramin, was initially tested as an anti-HIV agent several years ago at NCI. Although it was not useful as an inhibitor of HIV, further investigation has revealed that it is a potent inhibitor of human growth factors. This is an important finding because many tumors are thought to depend on the presence of small amounts of growth factors for continued proliferation. For example, NCI scientists recently reported that Kaposi's sarcoma cells produce fibroblast growth factor and

IL-1 which stimulate further growth of these tumors. Suramin has recently been shown to antagonize some of these Kaposi's sarcoma growth factors. NCI scientists have also recently identified compounds which may be less toxic than suramin and potentially even more effective inhibitors of Kaposi's sarcoma.

In the coming year, NCI scientists will continue to conduct clinical protocols testing new leads emerging from the AIDS Drug Discovery Program and new combinations of known effective agents in adults and children. Future clinical trials will include a Phase I trial of CD4-immunoadhesins, in addition to trials of antisense phosphorothioate nucleosides and anti-growth factor therapy with suramin and suramin analogs. Larger quantities of the CD4-PE protein are being produced by recombinant DNA technology which should enable the testing of this compound in an animal model in the very near future. Clinical research will also focus on the impact of AZT-resistant HIV and the efficacy of other nucleoside drugs in this setting.

Last year we noted that some of the target sites on the HIV envelope protein that have been most effective in eliciting an immune response appear to be located in a hypervariable region of the envelope protein, that region of the protein that varies with each strain of the virus and is most susceptible to mutation. Current investigations are underway to identify suitable peptides in a stable region of the viral protein so that a vaccine incorporating these peptides would provide protection against multiple strains of the HIV virus. NCI scientists will increase their efforts to identify peptides that can stimulate an effective immune response against the HIV virus and to determine how best to combine these synthetic peptides to produce a vaccine that is more efficacious than one produced from a single protein.

Many AIDS patients are latently infected with the human cytomegalovirus (HCMV), which, like HIV, can suppress the host immune system and infect human lymphocytes. Recent evidence indicates that HCMV and HIV may stimulate each other's growth. In order to define the interactions between HCMV and HIV in the development of AIDS and assess the role of HCMV as a co-factor in the progression of disease, transgenic mice (mice in which foreign genes have been added to the mouse's DNA) expressing HCMV regulatory genes will be mated with different transgenic HIV mouse lines and tissue specific expression of HIV and HCMV will be determined. This research may lead to an understanding of the interactions between the purported etiologic co-factors which cause worsening of the immunodeficiency disease.

There has been a dramatic increase in the appearance of dementias and other neurologic sequelae in AIDS patients. HIV is known to infect cells of neural origin and has been isolated from the CNS in patients with AIDS. FIV and FeLV will receive increased attention as models of these neurologic deficits associated with HIV infection of the CNS. The viral genetic basis for CNS infection will be examined, and the cellular and electrophysiologic anomalies caused by retroviral infection will be investigated. Research in this animal model may lead to an understanding of the mechanisms involved in the dementia and loss of neurological function in AIDS patients.

Thus, a number of retroviral-host systems are being explored as model systems for human HIV infections. Since a direct model of the human infection does not yet exist, it is fortunate that a number of other retroviruses with similiar properties are available to provide necessary information about the interactions of these agents with their hosts and about approaches to prevention and treatment of AIDS.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Research

Authorization: Indefinite

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
PROGRAM ACTIVITY:						
Cancer causation....	647	$447,396,000	659	$469,991,000	+12	+$22,595,000
Detection & diagnosis	162	116,909,000	163	121,365,000	+1	+4,456,000
Treatment research..	787	544,156,000	799	564,223,000	+12	+20,067,000
Cancer biology......	444	286,708,000	451	301,826,000	+7	+15,118,000
Total...............	2,040	1,395,169,000	2,072	1,457,405,000	+32	+62,236,000

MECHANISM:	No.	Amount	No.	Amount	Amount
Research projects.	3,119	$748,447,000	3,109	$784,686,000	+$36,239,000
Other research:					
Cooperative clinical research.......	189	59,747,000	189	59,747,000	
Minority biomedical research support		2,582,000		2,801,000	+219,000
Other research related.........	200	8,817,000	200	8,817,000	
Subtotal, other...	389	71,146,000	389	71,365,000	+219,000
Total, rsrch grants	3,508	819,593,000	3,498	856,051,000	+36,458,000
Research & development contracts...	394	198,099,000	394	201,796,000	+3,697,000
Intramural research		314,679,000		333,219,000	+18,540,000
Research management and support.....		62,341,000		65,866,000	+3,525,000
Cancer prevention and control.....	2	457,000	2	473,000	+16,000
Total, NCI........	3,904	1,395,169,000	3,894	1,457,405,000	+62,236,000

National Cancer Institute

Research

CANCER CAUSATION RESEARCH

Purpose and Method of Operation

The clinical appearance of cancer is the end result of a complex interplay of forces. External agents such as chemicals, radiation, fibers and other particles, viruses, parasitic infections, along with host factors such as hormone levels, nutritional and immunologic status, and the genetic endowment of the individual all contribute to the initiation and promotion of cancer. Cancer causation research, recognizing these interrelationships, includes investigations into chemical and physical carcinogenesis, biological carcinogenesis, epidemiology, chemoprevention and nutrition. Each of these scientific areas interacts with the other: epidemiology attempts to identify environmental and genetic risk factors; chemical and physical carcinogenesis research seeks to elucidate, at the molecular level, the ways in which chemical and physical agents trigger malignancy; biological carcinogenesis research uses viruses and cloned segments of the genome as investigative tools to examine and analyze the genes and gene products which can cause cancer; chemoprevention research identifies chemicals and other agents capable of either preventing or reversing the process of carcinogenesis at one or more stages; and nutrition research focuses on foods, nutritional factors, and dietary habits that may either induce, promote or inhibit cancer. Research findings in any one of these areas may shed light on a problem being investigated in another, for ultimately each discipline is concerned with the fundamental causes and prevention of human cancer.

Rationale for the Budget Request

The 1991 estimate of $469,991,000 represents an increase of $22,595,000 from the 1990 estimate. The program plans for 1991 are as follows:

CHEMICAL AND PHYSICAL CARCINOGENESIS - A 1991 estimate of $177,320,000.

The Multistage Process of Cancer Development

The development of several forms of cancer appears to occur in at least two steps: the initiation stage and one or more promotion stages. The initiation stage involves the interaction of a chemical with DNA in such a way as to alter its function. A single exposure can be sufficient to induce the initiated state, and this state is probably irreversible. Initiators include chemicals, fibers, radiation and viruses. Nutritional, hormonal, environmental and genetic factors can act as promoters. Promoters do not cause cancer directly; they facilitate the carcinogenic process. Progress made during the last several years in the development of methodology to culture human tissues and their epithelial cells from most major sites of human cancer has allowed initiators and promoters to be investigated at the tissue, cellular and subcellular levels of biological organization. An

Studies on the cytochrome P-450 family of enzymes will continue during the coming year, since a better understanding of their tissue distribution, activity, and regulatory controls has the potential of enabling identification of individuals who are unusually susceptible to carcinogens. Attempts to characterize the structure-function relationships among the cytochrome P-450s will be carried out during the coming year, as will examination of the factors governing the regulation of expression of the cytochrome P-450 gene family. The developmental profile and induction characteristics of P-450s and of several P-450 catalyzed activities will also be determined.

Normal human tissues and cultured bronchial epithelial cells and fibroblasts exhibit DNA repair activity _in vitro_ by catalyzing the repair of a mutagenic lesion produced by a type of reactive chemical known as an alkylating agent. This activity was found to vary in the different human tissues tested in the decreasing order of liver, colon, esophagus, lung, and brain. Formaldehyde was found to inhibit this repair process and also enhanced the mutagenicity of another alkylating agent in normal human fibroblasts. In some experimental studies, repeated exposure to alkylating agents led to an increase in DNA repair activity, with DNA repair thus appearing to be an adaptive response. The results of recent studies indicate that human bronchial epithelial cells do not adapt and increase their DNA repair capability. This finding may have important implications in carcinogenesis caused by low doses of alkylating agents.

The effects of cigarette smoke condensate and "smoke conditioned" media on the activity of different DNA repair enzymes in cultured human bronchial epithelial cells will be investigated. The activity of these DNA repair enzymes will also be measured in the alveolar macrophages and peripheral blood lymphocytes of smokers and non-smokers. The DNA repair capability of macrophages from smokers compared to non-smokers will be measured.

Information as to how and where carcinogens interact with DNA can provide clues as to the mechanism by which the carcinogen exerts its biological effects. Continued efforts will be made in _in vitro_ systems and in animals to identify, quantify and characterize the products of carcinogen-DNA interactions termed "adducts." Very sensitive immunologic techniques have been developed to detect carcinogen-DNA adducts in individuals exposed to various environmental carcinogens such as benzo(a)pyrene. Antibodies to carcinogen-DNA adducts have also been detected in sera from people exposed to benzo(a)pyrene. Due to the longevity of immunological memory, such antibodies may be useful as an indicator of exposure to carcinogens which occurred many years previously. The ability of these antibodies to be useful indicators of cancer risk will continue to be assessed.

The importance of DNA adducts in the carcinogenic process has been emphasized by investigations of DNA repair and DNA adduct removal. In most cases, enzymatic adduct removal is a crucial protective mechanism acting to offset the carcinogenic insult. When repair mechanisms are lacking, such as in the human disease xeroderma pigmentosa, tumorigenesis is accelerated. Complex mechanisms for repair of carcinogen-induced DNA damage are being

.identified in cells of different species and in response to particular classes of carcinogens; these studies will continue.

The Role of Oncogenes in Chemical Carcinogenesis

The identification of specific transforming genes (oncogenes) in both human and experimental tumors has stimulated intensive efforts in several laboratories to clarify the roles of those genes in the pathogenesis of cancer. Since many of the known oncogenes derive from normal elements of the mammalian genome, there is a real possibility that the biochemical mechanisms of neoplastic transformation may be defined by thorough analysis of the properties of the oncogenes and their cellular counterparts. Of special interest in chemical carcinogenesis are oncogenes, such as the ras family of genes, that behave as dominant genetic elements and that are activated to this behavior by a mutation in a single base of DNA. This mechanism of activation can be caused, in principle, by mutagenic chemical carcinogens, which can be provisionally identified as such by their genotoxic effects. The mechanism of action of such agents, long considered to involve damage to DNA, may eventually be reconciled with molecular virology, and the crucial events in cellular transformation by both chemical and biological agents, defined through analysis of the activation and behavior of oncogenes. Detection and critical evaluation of the roles of dominant oncogenes, especially mutant genes of the ras, erbB and neu families will continue to be an area of research in chemical carcinogenesis.

The expression of activated cellular oncogenes in chemically-induced tumors in rodents and in selected human neoplasms, and the relationship of oncogene expression leading to the progression from the normal to a neoplastic state are currently being studied. In addition, a newly developed technique, polymerase chain reaction (PCR), will be employed to amplify selected segments of the DNA chain in order to search for subpopulations of cells in a given tissue in which activating oncogene mutations may be present. Evidence indicates that such subpopulations of cells seem to occur naturally, with a point mutation in the ras gene, in the skin of a strain of mouse (SENCAR) that have been bred for high susceptibility to squamous papilloma and carcinoma induction.

Studies on Tumor Promoters

Tumor promoters, in contrast to tumor initiators, do not appear to interact with DNA; recent studies suggest that they act by modulating gene expression, growth and differentiation. By themselves they are not able to produce tumors, but they markedly enhance the formation of tumors when applied after exposure to an initiating agent. Multiple exposures to a promoting agent are generally necessary to be effective, suggesting that promotion is a reversible phenomenon. Tumor promotion has been demonstrated in in vitro systems and in experimental animals and there is reason to assume that it plays a role in human cancer as well.

Previously, the cellular receptor from one class of experimental tumor promoters, phorbol esters, was identified as the enzyme protein kinase C (PKC). The composition of this enzyme, its amino acid sequence, has also been determined. Several chemicals have now been shown to act as anti-promoters in a model system through their effects on PKC. Such studies should lay the groundwork for the development of anti-promoting agents with practical utility.

Cellular and Molecular Biology of Normal and Neoplastic Cells

The cellular and molecular mechanisms controlling growth and differentiation of normal animal and human cells is under intensive investigation and studies in this area will continue to be supported. Aberrations in these normal mechanisms can be studied *in vitro* in normal and neoplastic cell lines and also in laboratory animals. Comparisons between normal and neoplastic cells generate hypotheses that can be tested in carcinogenesis studies. In addition, cellular and molecular markers of normal versus neoplastic cells and selective conditions for growth have pragmatic value in carcinogenesis and chemoprevention studies and in cancer diagnosis.

Growth factors have been shown to play a pivotal role in molecular and cellular biology. Indeed, the current excitement in research about one such growth factor, transforming growth factor-beta (TGF-beta), comes from its multiple actions on almost every type of cell and its potential for therapeutic use in common clinical conditions for which there are presently no adequate pharmacological agents. Although TGF-beta was originally identified in an assay which measured its ability to enhance the growth of fibroblasts ("transformation"), its true importance is as a mediator of normal cellular physiology, in particular during normal formation of tissues (as in embryogenesis), as well as during their response to injury (as in inflammation and repair). Almost all cells have been shown to make TGF-beta in one of its molecular forms, and essentially all normal cells have receptors for TGF-beta.

TGF-beta has many actions. It can stimulate proliferation in some cells, especially in connective tissue, while it is a potent inhibitor of proliferation in others, such as lymphocytes and most normal epithelial cells. Moreover, it can regulate other processes which have little to do with cell division, such as the synthesis of collagen and other critical molecules of the extracellular matrix of bone, cartilage, and connective tissue. There is now extensive data on the role of TGF-beta during inflammation and repair. Platelets are the most concentrated source of TGF-beta in the body, and TGF-beta is released from them at sites of tissue injury. This process starts a cascade of events leading to tissue repair. The effect of TGF-beta on collagen synthesis is especially noteworthy, since it has been shown that TGF-beta enhances gene transcription for this molecule, which has such a critical role in providing the structural strength of healing wounds, as well as serving as an essential part of the matrix of bone and cartilage.

These actions are of obvious therapeutic relevance for potential clinical applications, including surgical wound healing in debilitated patients or those undergoing chemotherapy; treatment of diabetic, decubitus, and varicose ulcers; and treatment of burns. Animal studies have shown that TGF-beta can enhance wound healing in many experiments, but human use has not yet begun. An important new application has been the intra-ocular use of TGF-beta in experimental animals to promote retinal reattachment to the underlying tissue after retinal detachment, a common cause of human blindness. A vigorous basic research program will be pursued in this area as well as plans to utilize TGF-beta in clinical trials for wound healing or bone healing and to promote retinal reattachment.

Heterocyclic Amines and Cancer

During the past few years, a number of studies have shown that the cooking of meat, under certain circumstances, produces mutagens which may contribute to a person's risk for cancer of the stomach, large intestine, liver, or other organs. Of these mutagens, the most important are a group known as the aminoimidazoazaarenes (AIAs), also referred to as heterocyclic amines. Their importance derives from the fact that our exposure to them is highest, since they are formed at relatively low household cooking temperatures by grilling, frying and broiling meat. Although a number of related heterocyclic amine carcinogens can be formed by heating amino acids and foods, they are not produced under normal household cooking conditions (200 to 300 degrees centigrade).

A number of AIAs have been purified from cooked ground beef, a major protein source in the American diet. All AIAs characterized to date, with one exception (PhIP), have been shown to be very potent mutagens in a bacterial assay system known as the Ames test. PhIP is a relatively weak mutagen, but it is present in tenfold greater concentrations in cooked beef than any of the other AIAs, and is the most potent AIA in mutagenicity studies utilizing mammalian cells rather than bacteria.

Thus far only three of the AIAs, referred to as IQ, MeIQ and MeIQx have been evaluated in long-term rodent bioassays, and all three have been found to induce a variety of tumors including tumors of the liver, forestomach, and colon. Synthesis and characterization of the major DNA-IQ adducts and examination of DNA-IQ adducts in rodents and non-human primates is underway and the role of specific cytochrome P-450s in the metabolic activation of IQ is being evaluated. Several cynomolgus monkeys receiving daily oral doses of IQ at 10 or 20 mg/kg have been diagnosed with hepatocellular carcinoma. The latent period for tumor induction (three years) is similar to the latent period for liver tumor induction by diethylnitrosamine, the most effective liver carcinogen in non-human primates.

Because little is known about the mechanism(s) of mutagenicity and/or carcinogenicity of the AIAs, estimating their carcinogenic risk to humans is difficult. Uptake, metabolic activation, and clearance from the body and DNA adduct formation have been studied in detail only for IQ and only in rodents. These recent studies show that with metabolic activation of IQ, both DNA and serum protein adducts are formed, and IQ and its metabolites are excreted in the urine. Studies on IQ and other AIAs will continue using other species and human cells in culture.

Only a few studies have been performed thus far in humans, but all have demonstrated that mutagens and their metabolites are present in the urine of individuals eating fried meat. The specific chemicals responsible for the mutagenicity in these early studies were not identified. However, recent developments in both chemical detection, as well as detection using antibodies against the AIAs, will allow detection of specific AIAs in humans after consumption of fried meat. In addition, during the past year it was shown that a single type of cytochrome P-450 is responsible for activation of most, if not all, of the AIAs. Studies both in humans and animals have shown that this type of P-450 exhibits a high degree of individual variation and that its levels are increased by environmental pollutants such as cigarette smoke. This is of importance, since both risk and individual susceptibility to the mutagenic effects of AIAs may be directly related to the activity of this particular type of cytochrome P-450. Therefore, any risk estimation for an individual must consider both the level of exposure and how the individual metabolizes a particular chemical. By employing currently available methods for measurement of parent AIAs, their metabolites, and DNA adducts, it should be possible to obtain indices of both individual exposure and the response to that exposure.

Thus, research has now documented that during the normal process of cooking beef and other meat products, a number of heterocyclic amines are formed that have carcinogenic activity in animals. These compounds have been detected in human body fluids following consumption of cooked beef and other meat products. Using the standard categorization scheme employed by regulatory agencies, the AIAs are carcinogens, but their potential role in the etiology of human cancer is, at present, unknown. It is, however, clear that these chemicals are consumed by a large proportion of the population of North America and Western Europe. A method for the quantitative determination of various heterocyclic amines will be further developed. The available data indicate that the intake of heterocyclic amines per person per day is around 100 micrograms. The acquisition of further data will allow for an assessment of the risk which these heterocyclic amines pose for humans. In addition, research on the mechanism of action of this new class of mutagens and their interaction with cellular DNA will be expanded and studies are planned to evaluate the potential role these chemicals may play in the etiology of human cancer.

Studies Evaluating Cancer Risk Due to Radiation Exposure

Studies in radiation carcinogenesis investigate the biological effects of low doses of ionizing and non-ionizing radiation. It is anticipated that this research will provide new and relevant information on the molecular and cellular processes leading to mutagenesis, cell transformation and carcinogenesis by radiation. Fundamental biophysical and radiochemical investigations are supported as well as cellular and whole animal studies and several epidemiological investigations. A better understanding of the relationship between cancer risk and radiation, particularly risks associated with low-level exposures are important for regulatory decisions concerning the use of radiological and nuclear technology in medicine and industry, as well as for public health officials responsible for evaluating radiation effects as a means of cancer prevention.

Continued emphasis will be given to epidemiologic studies investigating the carcinogenic effects of ionizing radiation and special attention will be given to the relationship between radiogenic changes in chromosomes and cancer risk. Studies of cervical cancer patients found a significant dose-response for radiation-induced chromosome aberrations more than two decades after exposure. Data from other populations indicate that therapeutic or diagnostic doses of radiation, for a variety of conditions over a large age span, induce chromosome aberrations that can be detected as much as 40 years after exposure. Cytogenetic studies will continue in several populations under epidemiologic surveillance, including patients irradiated for tonsillitis, tuberculosis, thymic enlargement, cervical cancer, or benign gynecologic disease.

Chromosome aberrations will also be evaluated in cancer patients treated with neutrons to determine the relative biological effectiveness of high-LET radiation in inducing damage at the cellular level. These findings will be compared to chromosome damage in cancer patients treated with conventional x-rays. The technique of chromosome painting, which is a relatively new approach to assessing chromosome damage, will be employed.

To investigate causes of leukemia, the most common form of cancer in children, a collaborative case-control study will evaluate a variety of exposures, including electromagnetic radiation, ionizing radiation, and pesticides, along with various childhood illnesses and prenatal events. In a study coordinated by scientists at the University of Minnesota, ionizing radiation will be one of the risk factors evaluated in a case-control study of acute lymphoblastic leukemia in infants. Irradiation will also be examined as a risk factor in case-control studies of brain cancer, which are being carried out at the Fox Chase Cancer Center and the University of Southern California. At the University of Texas System Cancer Center, scientists will evaluate the risk of second malignancies among individuals who received radiotherapy for soft tissue sarcomas as children.

A study of cancer deaths in the vicinity of nuclear facilities in the United States will continue to be pursued. The study will determine whether residents of counties containing or adjacent to nuclear facilities have a higher risk of dying from cancer than residents of similar counties without nuclear facilities. The project was initiated because of public health and scientific concerns, especially after a survey of cancer mortality in areas around nuclear installations in the United Kingdom showed an excess of childhood leukemia.

Radon is an invisible, odorless radioactive gas produced from the decay of uranium in soil and rocks. When high levels of radon were detected in homes built on uranium-rich soil, concern arose about the potential adverse health effects on residents of these dwellings. Radon gas enters and accumulates indoors through cracks in concrete, floor drains, sump joints, small spaces in the soil and rocks, and by seeping in through dirt floors. Water drawn in from private wells may also be a source of radon. The accumulation of radon gas may be increased by the lack of ventilation and tight insulation. The radioactive by-products of radon can be inhaled into the lungs, where they lodge, causing damage to lung cells, which may lead to cancer. Studies of underground miners have shown a dose-response relationship between lung cancer and radon exposure at low levels. As a risk factor for lung cancer, radon pollution in homes will be evaluated in case-control studies that are nearing completion in New Jersey, Missouri, Sweden, and China.

BIOLOGICAL CARCINOGENESIS - A 1991 estimate of $163,289,000.

Biological carcinogenesis research supports studies on the mechanisms of carcinogenesis involving biological agents, viruses, and cellular genes at the biochemical, cellular, and molecular levels, utilizing sophisticated new approaches and techniques. Research is focused upon understanding how certain basic biological processes such as differentiation and proliferation are controlled in normal cells, and how these processes are altered during tumor formation. Major emphasis continues to focus on gaining a better understanding of the role that DNA and RNA viruses play as causal factors or co-factors in cancer.

DNA Viruses and Human Cancer

Interest in DNA viruses continues to expand as additional viruses are linked as factors or co-factors in human cancer or as models for human cancer. Viruses under study include human papillomaviruses (HPVs), hepatitis B virus (HBV), non-A non-B hepatitis virus (NANBH, also recently called hepatitis C virus), adenoviruses and Epstein-Barr virus (EBV).

Cervical carcinoma is a common malignancy among American women, and a leading cause of cancer deaths worldwide. Cervical cancer and certain malignancies of the vulva and penis are strongly associated with human papillomavirus (HPV) infections, which are common in the general population. The initial HPV infection is characterized by non-cancerous, wart-like growths. Eventually, in some individuals, these non-malignant growths will progress to cancer. The extrinsic factors which are necessary to cause progression to cancer are not yet known. An expanded emphasis is planned for studies to determine both the nature of these cancer causing factors and their interactions with papillomaviruses to induce cancer. These studies should aid in the development of methods either to prevent or treat HPV-associated cancers.

Individuals may be protected from HPV-associated cancers by preventing the initial HPV infection, or by altering the host response in such a way that the initial infection does not progress to malignancy. One way to accomplish these goals is by the development of safe and effective HPV vaccines. Prototype animal vaccines can prevent papillomavirus infections in animals and in some cases appear to promote the regression of existing infections and tumors. More information is needed, however, about the way the human body mounts an immune response against papillomavirus-infected cells before human vaccines can be prepared. Expanded research on the host response to HPV infection will be encouraged in order to lay the groundwork for the future development of human HPV vaccines.

Primary hepatocellular carcinoma, a form of liver cancer, is one of the most frequently occurring human cancers worldwide, and is responsible for approximately one million deaths annually. The greatest single risk factor for the development of this cancer is chronic carriage of the hepatitis B virus (HBV). It is estimated that there are approximately 200 million chronic carriers of HBV worldwide, and it appears that all persons who remain hepatitis B virus surface antigen carriers may eventually develop primary hepatocellular carcinoma. It is important to develop methods for preventing the occurrence of cancer among this high-risk group, for whom vaccines are not usable since they are already chronically infected. Furthermore, the reported emergence of HBV variants resistant to current vaccines is a recent development which could have serious consequences for the long-term prevention of new cases of hepatitis, and thus, ultimately for chronic hepatitis and liver cancer. Investigations are planned to verify the existence of these resistant variants and to attempt to determine the magnitude of this problem.

In addition, newly available data support the association of the non-A non-B hepatitis virus (NANBH) with liver cancer, particularly in Japan. Studies of this virus have been difficult in the past, since no specific test was available for its identification. Investigations on the role of NANBH in cancer will be facilitated by the recent availability of probes for the NANBH virus. Because of the significant incidence of non-A non-B hepatitis in the United States and the propensity for chronic infection with this agent, an expanded effort encouraging investigations on the role of NANBH in primary hepatocellular carcinoma will be initiated this year.

An increased level of activity will focus on other aspects of liver cancer, including systematic studies of interactions between viruses and dietary factors and/or chemicals as causative factors in primary hepatocellular carcinoma. Since there are apparently no viral oncogenes associated with the hepatitis B virus, the role of cellular oncogenes and anti-oncogenes in virus-associated liver cancer will be studied. Host factors relating to pathogenesis of liver cancer, such as genetic predisposition, chromosome abnormalities and/or fragility, and the immune response are other areas in which increased research is anticipated. Although the development of a safe and efficacious recombinant vaccine for HBV should result in a long-term decrease in new cases of liver cancer, the potentially serious problems with viral variants, and with individuals who do not respond to current vaccines with protective levels of antibody, support the need for continuing studies of the immune response.

Adenoviruses serve as a model system for viral oncogenesis because they can cause tumors in animals and the transformation of cultured cells. A particular adenovirus gene, designated E1, is primarily responsible for the virus's ability to cause tumors. Recently, it was found that another part of the viral DNA, designated E3, may also play an important role in tumor formation. The latter region encodes three proteins which alter the properties of virus transformed cells. Two of these proteins make the transformed cells more resistant to attack by the host's immune system, and the third appears to influence the transformed cell's growth. Future studies of the mechanism of action of these viral proteins should provide insights into the mechanisms of viral transformation and lead to strategies to control or reverse these changes.

Epstein-Barr virus (EBV) is a herpesvirus which has been associated with several diseases including infectious mononucleosis, Burkitt's lymphoma and nasopharyngeal carcinoma. Over 80 percent of the world's population is infected with EBV. The virus remains latent in most individuals, causing no obvious illness. However, in individuals whose immune system is damaged, either by certain infectious agents, such as human immunodeficiency virus, or by treatment with immunosuppressive therapies for cancer or organ transplantation, virus-infected cells appear to grow into B-cell tumors. An increased understanding of the pathogenesis of EBV has come from recent molecular biological studies of the virus DNA which have identified a regulatory virus sequence (transactivator) and two responsive EBV DNA sequences involved in the transition from latent to active EBV infection. Each of the two responsive elements is active in different types of tissues. Although the tissue site of EBV latency has not yet been determined, recent molecular studies of the types of EBV virus present in bone marrow transplant recipients have suggested that the virus may be latent primarily in blood (hematopoietic) tissues. If this is true, it may be possible to devise methods to eradicate EBV infection by physical or chemical procedures, since blood cells are more accessible to such procedures than solid tumors. Future studies will continue to focus on the mechanisms by which EBV remains latent or becomes reactivated with the goal of preventing and controlling reactivation in immunocompromised individuals.

Infection with human herpesvirus-6 (HHV-6, also called human B-cell lymphotropic virus) has been associated with a variety of growth disorders of immune cells as well as with lymphomas and lymphocytic leukemia in young children. The virus was originally isolated from patients with a variety of hematological disorders including AIDS. More recently, it has been isolated from healthy blood donors and from infants with roseola. It has been found that about 55 to 60 percent of the general population of the United States, Canada, and Europe have HHV-6 antibodies, which suggests that, like other herpesviruses, HHV-6 is endemic and latent in the population. HHV-6 is a completely new member of the human herpesvirus family, differing from other herpesviruses by both immunologic and molecular analysis. Studies to define more sharply the etiologic role of HHV-6 in specific lymphoproliferative and immune abnormalities in humans will be supported. The recent finding that HHV-6 can replicate (multiply) in a diversity of cell types, including both B and T lymphocytes at different stages of maturity, suggests an even broader role for this virus in various blood disorders. Further, it has recently been found that cells infected with HHV-6 produce a factor, or factors, that bind to the AIDS virus, HIV-1, and trigger it to replicate. This finding is of importance because it strongly suggests that HHV-6 may play a role in the progression of AIDS.

Retroviruses

Retroviruses (RNA viruses) have been identified as causative agents of naturally occurring diseases in many species, including humans. These diseases include various forms of cancer (leukemias, lymphomas, sarcomas, carcinomas), neurologic disorders, and wasting syndromes. In most cases, the causative virus is acquired as an infectious agent, rather than one transmitted in the germline from parent to offspring. Retroviruses have been increasingly associated with a variety of human diseases in the last few years, although initial attempts to isolate them from human tissue were futile.

The most frequent disease induced by the human T-lymphotropic virus type 1 (HTLV-1) is a cancer in adult humans known as adult T-cell leukemia (ATL) which occurs through the malignant conversion of a subset of immune cells known as T-lymphocytes. ATL was first described in Japan where clusters of this cancer were observed. This disease shares some clinical features with other T-cell malignancies such as Sezary syndrome, mycosis fungoides, and chronic T-cell leukemia, but is also distinct from them.

HTLV-2, a variant of HTLV-1, has been isolated from several cases of a form of cancer of T-lymphocytes known as hairy cell leukemia. Although tumor cells from each of these patients appear to be infected with the HTLV-2 virus, thus suggesting infection prior to development of leukemia, at present there is insufficient epidemiological data to link the virus to this or any other specific disease.

Substantial evidence implicates retroviruses in the etiology of spontaneous T-cell lymphomas in mice, and recent studies indicate that retroviruses may play an etiologic role in other types of lymphomas and leukemias as well. Leukemia-inducing retroviruses are thought to induce cancer in their hosts by inserting their genomes into the host cell chromosomes, adjacent to a cellular proto-oncogene, thereby causing a change in the way the proto-oncogene is regulated. In an inbred strain of mice known as AKR, more than 90 percent of animals surviving to one year of age will develop myeloid leukemia. A retrovirus has been isolated from these mice, and was recently shown to induce granulocytic leukemia in experimentally infected mice. Recent mechanistic studies of this retrovirus indicate that it apparently activates a hitherto unknown oncogene on mouse chromosome 11. This new proto-oncogene has also been found in human DNA, and researchers are now trying to localize it to a specific human chromosome. Future studies will determine the possible role of this new human proto-oncogene in human cancer.

Studies of one of the genes of an avian tumor virus have provided a novel method which can be used to produce large quantities of biologically important proteins. A major difficulty in producing large quantities of proteins in mammalian cells has been the contamination of the desired protein by the large amounts of serum proteins which are necessary in the cell growth medium. Retroviral vectors have been constructed in which a viral gene is linked to the gene for the protein of interest. This technique results in the production of a molecule containing the two proteins linked together (fusion protein) which then migrates to the cell surface. Interaction of the normal viral proteins with one another results in virus budding. As a consequence, the fusion protein becomes enclosed in a membrane from which other contaminating cytoplasmic proteins are excluded. As the budding process nears completion, the protein of interest becomes cleaved from the retrovirus protein by a cellular enzyme. The enveloped particles are then released into the cell growth medium and can be purified by centrifugation in the same way that a retrovirus can be purified. The particles are not infectious, are safe to handle, and offer a convenient means of large-scale protein production in mammalian cell systems. This technique, called "retro-secretion," is currently being patented by the grantee institution. It is a promising method for producing a broad variety of proteins of biomedical interest whose properties and characteristics can be studied. Further investigations should result in other potential applications of molecular biology to the resolution of problems in biomedical research.

Oncogenes

Major advances are being made in the study of oncogenes as growth factor receptors, and a novel growth factor (keratinocyte growth factor) which is active on a variety of epithelial cells has recently been purified and molecularly cloned. Additional efforts will be devoted to exploration of the ways in which cell proliferation is triggered by this substance, and to cloning its receptor. This would allow a more detailed study of the potential for overstimulation of this growth factor pathway in cancer and other proliferative states. Alternatively, the possible application of the factor in situations where epithelial proliferation is specifically desired, such as the healing of burn wounds, will also be explored. Additionally, a second new growth factor with epithelial specificity has been isolated, and investigations of its properties are also planned as part of expanded studies on oncogenes and growth factor receptors designed to elucidate their possible role in cancer.

A second class of cellular proteins which are important in oncogenesis has been revealed by studies of the familial inheritance of cancer and of the transforming proteins of several small DNA viruses. These proteins are called anti-oncogenes or suppressor oncogenes, because the absence of a functional gene product, rather than its presence, is responsible for transformation. One of the best understood examples of suppressor oncogenes is the Rb gene of retinoblastoma, whose loss or inactivation appears to play an important role in the induction of retinoblastoma. Inactivation of the Rb gene may also play a role in some other commonly occurring cancers of the lung and colon. Loss or inactivation of both copies of the Rb gene in humans may predispose an individual to cancer. It was recently found that loss of both copies of the Rb gene in retinoblastoma tumors results in loss of cellular response to the growth inhibitory substance, transforming growth factor beta (TGF-beta). Current studies are aimed at determining whether this loss of responsiveness resulted from the loss of the cellular receptors for TGF-beta. These observations may explain the transformed phenotype of retinoblastoma cells.

A second observation which related inactivation of the Rb protein to oncogenesis resulted from studies with three groups of DNA viruses. Adenoviruses, papillomaviruses, and polyomaviruses all encode specific viral oncogenic proteins responsible for the malignant transformation of infected cells. Some of these same viral transforming proteins have been demonstrated to bind tightly to the Rb protein. Since cancer is promoted by the loss or inactivation of the Rb gene, and consequently of functional Rb protein, the simplest hypothesis for oncogenesis by these viruses is that inactivation of the Rb protein results from the formation of a complex between viral transforming proteins and the Rb protein. Further studies of the interaction of RNA and DNA viral oncogenes with the Rb protein will seek to determine which of the many oncogene proteins produce cancer via interaction with suppressor oncogenes rather than by their own, direct effects and may suggest means of preventing or reversing malignant conversion. An additional suppressor oncogene has been identified in studies using the small DNA tumor virus SV40. This suppressor oncogene, designated p53, was able to inhibit transformation by pairs of oncogenes that normally would transform cells. One way in which the transforming protein of SV40, T-antigen, may transform cells is by binding to and inactivating the p53 protein. Further studies of this virus model may provide a simple method of identifying new cellular suppressor oncogenes and studying their role in preventing tumor formation.

EPIDEMIOLOGY - A 1991 estimate of $85,996,000.

The Epidemiology Program will continue to conduct studies to identify environmental, lifestyle, and host determinants of cancer in humans. The objectives of these studies are to understand the distribution and origins of cancer, the factors that predict cancer risk, and the means for preventing cancer. To accomplish these objectives, a wide range of studies is undertaken to develop and test hypotheses on the etiology and prevention of cancer. Attention will be given to descriptive studies to determine the demographic and geographic patterns of cancer, as well as time trends in cancer incidence and mortality. These hypotheses-generating studies often provide etiologic clues that can be pursued in studies using more rigorous analytical methods. For example, the development of U.S. cancer maps revealed geographic patterns of particular cancer types by small geographic areas. More focused analytical studies will continue to be undertaken to identify reasons for unusual patterns or elevated risks in certain parts of the country.

Occupational Studies in the Detection of Cancer Risks

Epidemiologic studies of occupational groups will continue to be pursued, since they have proven to be an important means of identifying environmental carcinogens, as well as industrial processes associated with increased cancer risk. Because certain occupational groups may be exposed to potentially hazardous substances in greater amounts and for longer periods than the general population, their cancer risks are often more readily apparent. Emphasis will be placed on occupational studies in which industrial hazards are suspected on the basis of experimental, clinical, and field observations. To stimulate research related to exposure assessment, a Request for Applications (RFA) was issued, which should result in a number of awards to extramural investigators for quantifying exposures at the cellular and molecular levels.

Evaluation of cancer risks among occupational groups with pesticide exposure will continue to be a major focus. Several studies were prompted by elevated rates of lymphatic and hematopoietic cancers among farmers from several mid-western states. In Kansas and Nebraska, the risks were especially high among farmers exposed to phenoxyacetic acid herbicides. These associations, particularly the relationship between non-Hodgkin's lymphoma and the herbicide 2,4-D, will be examined in further studies involving the agricultural use of pesticides. Other investigations will assess hazards that may be posed by exposure to various insecticides, herbicides, and grain fumigants among urban pesticide applicators and lawn care workers, aerial applicators, noxious weed applicators, and grain handlers.

A variety of investigations will be pursued to evaluate the contribution of occupational exposures to lung cancer risk. One study found that mortality from lung cancer was elevated among workers employed in a plant producing chromium pigments. In a study of Chinese iron ore miners, the risk of lung cancer among underground miners exposed to radon and silica was four times that of above-ground miners. A study is underway to evaluate the risk of lung cancer from silica exposure among workers employed in dusty trades in North Carolina. A complementary study will examine lung cancer risks among a group with silicosis and another group without silicosis but heavily exposed to silica.

Environmental Exposures and Cancer Risks

Epidemiologic efforts will continue to define cancer risks associated with general environmental exposures. An increased bladder cancer risk was found to be associated with the level of intake of chlorinated tap water, with long-term consumers having the greatest risk. To clarify these findings, a new case-control study will investigate cancer risks at six anatomic sites, including the bladder. Data from the first phase of this study are now being analyzed, with emphasis on the influence of agricultural chemicals and chlorination by-products as cancer risk factors.

The importance of air pollution in lung cancer risk will continue to receive attention. A case-control study in Shenyang, China, where pollution levels from home-heating stoves and industrial sources are among the world's highest, will continue to investigate the role of air pollution on the risk of lung cancer. A three-fold increased risk of lung cancer was found among male workers and residents near the Shenyang copper smelter, which releases inorganic arsenic and other metallic pollutants. Risks of lung cancer, especially among females, also rose in proportion to indices of indoor air pollution from coal-burning stoves.

Ultraviolet (UV) radiation will continue to be investigated as an important cause of melanoma and non-melanoma skin cancer. In melanoma, childhood and intermittent (recreational) exposures and sunburning are especially important, while in other skin cancers, cumulative (occupational) exposures play a key role. Predisposing host factors in the form of skin complexion for all types of skin cancer, and dysplastic nevi for melanoma, will continue to be clarified. Since sunlight is the major source of UV radiation and there is concern about stratospheric ozone depletion, UV exposures and skin cancer incidence will continue to be monitored.

Menopausal Hormones and Cancer Risk

The risks and benefits from the use of menopausal hormones continue to be of major interest. In a collaborative cohort study of 23,000 Swedish women who used menopausal hormones, an excess risk of endometrial cancer was noted for estrogens unopposed by progestational agents. Evaluation of breast cancer risk revealed a 60 percent increase in breast cancer after 10 or more years of replacement estrogen therapy, which was not diminished by the addition of progesterone to the regimen. The Swedish cohort and other populations will continue to be followed to examine the relation of menopausal hormone regimens to cancer and to non-neoplastic diseases, such as osteoporosis and cardiovascular disease.

At the University of Southern California, a prospective study will investigate health-related and lifestyle practices on a variety of cancers, including those of the bladder, breast, and colon, among adults aged 60 years or older in a Los Angeles retirement community. One outcome of the study will be an evaluation of the long-term risks and benefits of estrogen replacement therapy.

Familial Cancer Syndromes

Family cancer syndromes continue to be an important source of clues as to mechanisms of host susceptibility. Recent important findings include localization of the gene for the more common form of neurofibromatosis (NF-1) to the long arm of chromosome 17, and the less common form (NF-2, acoustic neuromas) to the long arm of chromosome 22. An ongoing multifaceted clinical and laboratory study of both forms of NF will further clarify importar aspects of these conditions.

Cutaneous malignant melanoma is one of the most rapidly increasing cancers in the white population in this country and worldwide. Recent epidemiologic studies have shown that an increased number of moles is an important risk factor for melanoma, with dysplastic moles (nevi) being the main precursor lesion. Approximately 10 percent of melanomas occur in individuals with a family history of melanoma, and about half of these arise in the five to eight percent of the general population who have dysplastic nevi. In collaboration with laboratory investigators, recent evidence indicates that the melanoma susceptibility gene is localized to a site on the short arm of chromosome 1. Attempts will be made to confirm the localization of the melanoma susceptibility gene in high-risk families and to develop new DNA probes closer to the actual gene site. These efforts are directed toward the goal of isolating and characterizing the gene's function and product so as to elucidate the mechanism of melanoma susceptibility and provide information useful for designing approaches to treatment and prevention.

Recent findings from studies of colo-rectal cancer has stimulated interest in investigations of diet, physical activity, genetic predisposition, and other risk factors. Using recently developed laboratory techniques, investigators are conducting genetic analyses of colo-rectal cancer and its precursor phenotype, the adenomatous polyp. It is expected that a number of other studies of colo-rectal cancer, with emphasis on the evaluation of nutritional and genetic determinants of this disease, will be undertaken through awards to extramural scientists.

Cancer Risks in Minorities

Emphasis will continue to be given to investigations aimed at explaining why Blacks Americans and other minority groups have elevated rates of certain cancers. A series of population-based case-control studies will investigate the reasons for blacks having higher rates than whites for multiple myeloma and cancers of the pancreas, esophagus, and prostate. Laboratory analyses for certain biochemical and immunological markers (e.g., hormones, micronutrients, trace metals, and HLA phenotype) will be performed to clarify the influence of lifestyle, environmental, and genetic factors in the elevated risk of these cancers among Black Americans. Other studies will clarify risk factors responsible for the high rates of lung, stomach, oral cavity, and cervical cancers in the black population. Reasons for elevated risks of breast cancer among black women at premenopausal ages will be investigated.

In a multicenter case-control study coordinated by investigators at Stanford University, risk factors for prostate cancer will be evaluated among blacks, whites and Asians in Los Angeles, San Francisco, Hawaii, Vancouver, and Toronto. At the University of Southern California, a case-control study of multiple myeloma will be carried out among whites and blacks in Los Angeles. At the University of Hawaii, studies will clarify risk factors for a variety of cancers that occur excessively among native Hawaiians.

An atlas of maps is being completed that displays geographic patterns of cancer mortality, for a variety of anatomic sites over three decades from 1950 to 1980, among the non-white population by state economic areas. These maps will highlight geographic areas having unusual variations and trends in cancer risks among non-whites, and provide etiologic leads that can be evaluated by more definitive epidemiologic studies. Preliminary findings indicate that, like the earlier maps for the white population, there is a tendency toward greater uniformity of rates around the country. An exception is the increasing concentration of prostate cancer among Black Americans in the southeastern part of the country, with clusters of high-rate areas emerging recently in the Carolinas.

NUTRITION - A 1991 estimate of $42,044,000.

Evidence continues to accumulate from epidemiologic and experimental studies that dietary and nutritional factors contribute to a significant portion of cancer in humans. Evidence for the role of dietary and nutritional factors comes from large international variations of cancer incidence, and from studies of migrants, whose cancer rates approach those of the host country during the process of acculturation. Emphasis will continue to be given to investigations to identify and evaluate specific dietary constituents involved as cancer risk factors.

Breast cancer mortality rates among women in China and Japan are about one-fifth those of white American women. Among successive generations of Asian women who have migrated to the United States, however, breast cancer rates have increased to approach those prevailing among Caucasians. The rising trend is suspected to be related to a gradual adoption of an American diet, which is high in meat, fats and calories. This hypothesis will be tested in a population-based case-control study of breast cancer among American women of Asian ancestry living in Los Angeles, San Francisco, and Hawaii. Detailed dietary histories have been collected to assess the role of nutritional risk factors, especially in childhood and adolescence. In blood samples, lipoproteins, fatty acids, micronutrients, and endogenous hormones will be measured to evaluate their relationship to breast cancer risk. In a separate investigation, a large-scale, case-control study of breast cancer will assess a number of possible risk factors, including the role of adolescent dietary patterns and alcohol consumption. In a study at the University of California at San Francisco, the risk of breast cancer will be investigated in relation to constituents of breast fluid secretions and to dietary factors among Chinese-American women.

Investigations into the patterns of cancer among Asian-Americans will be supplemented by studies conducted in their ancestral countries. For example, stomach cancer afflicts Japanese- and Chinese-Americans much more often than Caucasian Americans. In a high-risk area of China patients with stomach cancer were found to consume more salted foods and local sour pancakes, and less fresh vegetables than controls. Protective effects were noted for vegetables of the allium class, including garlic and onions. A case-control study of stomach cancer in high- and low-risk areas of Italy also revealed protective effects related to the intake of garlic and other fresh vegetables.

To evaluate the role of diet on precancerous lesions of the stomach (i.e., chronic atrophic gastritis, intestinal metaplasia, and dysplasia), subjects in the high-risk area of China are being enrolled in a screening program to detect early cancers and to contrast questionnaire responses with biochemical marker data. In another investigation, scientists at Stanford University are coordinating a collaborative case-control study of colon cancer among Chinese in both China and the United States.

Esophageal cancer also occurs more often among Chinese-Americans than Caucasian Americans. Dietary factors will be evaluated in Linxian, China, which has the world's highest rates of this cancer. In collaboration with scientists in China, a large-scale, five-year randomized intervention trial continues to evaluate whether certain groups of vitamins and minerals can inhibit late-stage progression to cancer in a high-risk population with multiple micronutrient deficiencies. One component of the trial focuses on persons with esophageal dysplasia and another on villagers from the general high-risk population.

A multicenter case-control study of endometrial cancer in the United States will focus on dietary components as possible risk factors. The dietary interview is designed to measure intake of all major nutrients, with a special emphasis on fat. Anthropometric measurement data will be used to evaluate the role of obesity, height, weight, and physical activity at various ages. Hormone assays will be carried out on blood samples to assess the relationship of obesity, diet, endogenous hormones, and cancer risk. Fatty acid profiles of plasma, red blood cells, cheek cells, abdomen and arm aspirates, and surgical abdominal fat will also be determined on a sample of the subjects.

A recent NCI study found that colo-rectal cancer cases were more likely than controls to have stool mutagenicity. This finding is intriguing, since heterocyclic arylamines are formed from the pyrolysis of amino acids when red meats are cooked at high temperatures by broiling, baking or frying. Although their biological effects in humans are unknown, a number of these substances are mutagenic in the Ames test (Salmonella TA98) and carcinogenic in laboratory animals, producing tumors of the liver, small intestine, and colon. Using a case-control approach, the relationship between mutagens produced during cooking and the risk of colo-rectal cancer will be investigated. Seventy patients with newly-diagnosed colorectal cancer are being compared to 114 controls with regard to usual diet, immediate past diet, cooking practices, and fecal mutagenicity.

Evaluation of Chemoprevention Agents

Chemoprevention refers to the administration of chemical agents to prevent the sequence of events that follows the exposure of an animal or person to a carcinogenic agent that results in the development of a malignancy. It involves the administration of naturally occurring or synthetic substances into the diet for the purposes of reducing cancer incidence. The areas of emphasis in chemoprevention will be to identify and evaluate new compounds showing biological activity in experimental systems; to synthesize more potent and less toxic compounds; and to initiate additional dose-setting and controlled clinical trials in chemoprevention.

The National Collaborative Chemoprevention Projects will continue this year and additional projects will be supported. These collaborative projects are designed to acquire basic knowledge in significant biological systems for anticarcinogenesis. A multidisciplinary approach is being employed in order to derive new insights into practical means for prevention of the process of carcinogenesis and to translate this knowledge rapidly into new chemopreventive entities with known ranges of efficacy and defined pharmacologic and toxicologic properties.

The Cancer Prevention Awareness Program

Since 1984, NCI's Office of Cancer Communications has conducted the Cancer Prevention Awareness Program, a major effort to increase public awareness of the possibilities for cancer prevention. It presents a challenge to the American people to learn what they can do on a daily basis to control their own cancer risks. The program offers specific tips for individual action based on the most recent scientific information related to cancer and prevention.

The objectives of this program are three-fold: to improve public attitudes regarding cancer incidence, treatment, and prevention; to improve public awareness and knowledge of cancer risks and of individual actions that control some of those risks; and to encourage individuals to adopt healthy behaviors to reduce their cancer risks and help detect cancer early. In addition to the overall public-awareness component of the program, intensified program efforts currently focus on two risk factors -- tobacco and nutrition -- and on one population group -- Black Americans -- because these areas offer the greatest potential for reducing cancer risk and influencing the cancer death rate. In addition, NCI launched a nationwide breast cancer screening education program in October 1989 at the Women's Leadership Summit on Mammography, an event cosponsored by NCI and the Susan G. Komen Foundation.

Breast cancer screening education efforts focus on two audiences: health professionals and women over 40. NCI is working to inform professionals of recently established consensus guidelines on mammography and encourage them to refer women 40 and over for routine screening mammograms. NCI also is mounting a public education campaign for women to inform them about the importance of mammography, dispel misconceptions about the procedure, and encourage actual use of mammography. Key communication channels include the mass media and organizations with large constituencies of women over 50. Special activities are underway to provide follow-up communications and tailored materials to the 60 key organizations represented at the Leadership Summit.

The general prevention awareness program relies on mass media and the Cancer Information Service (CIS) as primary avenues for the dissemination of its messages. Activities have included development of electronic and print media messages, distribution of printed materials, promotion of the toll-free CIS number 1-800-4-CANCER, and development of Partners in Prevention, a network of about 2,000 individuals and organizations involved in community-based prevention activities.

The prevention awareness program for Black Americans capitalizes on institutions and networks that reach black audiences in both urban and rural areas. The program uses the mass media and the Joint Health Venture to develop and deliver its messages. The Joint Health Venture, part of Partners in Prevention, is a network of national and regional civic, religious, education, and professional groups working with the NCI to disseminate cancer prevention information to members of the black community. OCC also is supporting community-based cancer prevention activities through five master agreement projects in New York, Philadelphia, Houston, Detroit, and the state of Illinois. Similar communication activities are being planned and conducted to reach hispanic Americans with cancer prevention information and to reduce fear and fatalism associated with cancer in this population.

Information and education activities in the tobacco education program are targeted to two groups: the general public, to increase awareness of the risks of tobacco use and to encourage cessation among users; and health professionals, to enhance their involvement and skills in counseling patients about smoking cessation and cancer prevention. Special efforts are being made to package and disseminate the results of NCI-supported tobacco intervention research in the form of practical how-to manuals for health professionals, educators, media advocates, and other tobacco control activists.

The focus of the nutrition education program is on increasing awareness in the general population of the link between diet and cancer and on providing clear, practical advice about changes individuals can make in their own diets to increase fiber intake and reduce fat intake. Program messages are targeted to the "household food manager," and numerous activities are underway to enlist health professionals and food and nutrition organizations in promoting messages and materials. Special efforts are being made to develop strategies and materials for a nationwide supermarket education program, particularly in regions serving large minority, low-income, and blue-collar populations.

DETECTION AND DIAGNOSIS RESEARCH

Purpose and Method of Operation

Research on detection and diagnosis is aimed at improving diagnostic accuracy, characterizing the behavior of tumors more completely to aid in prognostic and therapeutic decisions, monitoring more effectively the response to therapy, detecting recurrence of cancer earlier, and identifying populations at increased risk of developing cancer. The accuracy of diagnosis, which includes improved classification of tumors, and the precision of pathologic staging are critical for the physician in choosing the most effective therapeutic approaches. The ability to monitor the response to therapy and to detect disease recurrence as early as possible allows the physician to assess the choice of therapy and to make appropriate modifications. Identification of individuals and populations at increased risk should result in more targeted screening programs and the earlier detection of tumors.

The field of diagnosis research currently is focused on the search for tumor markers, the measurement of the amount of DNA in the nucleus (cell ploidy) and of other cell cycle characteristics, the measurement and evaluation of specific genetic alterations in tumor cells, and the improvement of imaging techniques. More specific antibody reagents are being developed to identify tumor markers in tissue sections and in body fluids, and efforts continue to identify new, more informative markers. The value of measurements of DNA ploidy by flow or image cytometry is being investigated for diagnosis, monitoring of therapy, detecting recurrence, and prognosis. Applications of genetic technologies to cancer diagnosis have added another dimension to classical histopathology. Investigators are looking for cytogenetic alterations that correlate with specific tumor types or with tumor progression and others are using molecular genetic analyses to assess correlations of specific oncogene activation or amplification with various clinical parameters. Improvements in diagnostic imaging techniques have resulted in the ability to detect smaller tumors and provide better staging information.

Rationale for the Budget Request

The 1991 budget estimate of $121,365,000 represents an increase of $4,456,000 from the 1990 estimate. The program plans for 1991 are as follows:

EPIDEMIOLOGY - A 1991 estimate of $11,933,000.

The Surveillance Program

The primary direct measures of cancer are incidence (the rate at which new cancer cases occur), mortality (the rate of cancer deaths), and survival (the likelihood that a person survives for a particular length of time following a cancer diagnosis.) These measures are collected through NCI's Surveillance, Epidemiology, and End Results (SEER) program for incidence and survival and through the National Center for Health Statistics (NCHS) for mortality. Data on population size for various ages, sexes, and racial groups in specific geographic areas are obtained from the Bureau of the Census.

The SEER program began in 1973 and provides comprehensive cancer data from nine registries encompassing some 10 percent of the population of the United States. Although the SEER program provides excellent coverage of whites in America, coverage of Black Americans and other minorities, as well as Americans living in rural areas, needs to be increased to improve the amount of information available for detailed analyses. During FY 1991, the Institute plans an expansion of the SEER program to add an increased base in Black Americans and Hispanics. Because the full spectrum of cancer incidence and mortality for rural areas is not known, NCI also plans to increase coverage of people who live in rural areas, particularly rural agricultural areas, in the SEER program. In addition, an expansion in the data collected concerning cancer care, particularly patterns of early detection of cancer and patterns of treatment is anticipated. Plans are to initially address breast cancer along with several other major cancers, such as cancer of the colon, prostate and melanoma.

The growth in cancer registration outside of the SEER program has been significant over the last decade. Much of this growth has been prompted by the need for regional data to develop profiles of cancer problems as the basis for subsequent cancer control interventions. During FY 1991, the SEER program will continue participation in evaluation activities to enable local registries to compare and contrast their data with the SEER National Profile and, thereby to develop a more accurate assessment of regional cancer problems. Technical assistance for assuring complete case ascertainment and other quality control activities related to measuring cancer incidence will be provided.

During FY 1991, the Surveillance Program will concentrate on preparations for two large surveys to be conducted in FY 1992. Plans will be developed and questionnaires field tested for a follow-up to the 1987 survey conducted through the National Health Institute Survey (NHIS). The NHIS provides indirect measures of cancer control, such as the prevalence of smoking and various dietary patterns and public behavior toward cancer prevention and early detection. In addition, the Institute will plan a major survey for 1992 on physician attitudes and behavior with respect to smoking, dietary, and early detection interventions, and referrals to cancer treatment and clinical trials.

The cost of cancer control programs is a significant factor in their development and application. In a study planned for 1991, the Institute will assess the cost of cancer control as well as the cost of treatment, along with the economic impact of cancer morbidity and mortality.

A portion of the Surveillance Program is devoted to research on improving the monitoring of cancer both for direct and indirect measures, and on improving the analysis of cancer trends. Plans for FY 1991 include an expansion of the analytic effort devoted to cancer surveillance. Initiatives will be directed to enlist the epidemiology and statistics community in conducting research on specific issues in cancer trends, notably, the influence of early detection on cancer mortality, the assessment of rates of diffusion of new cancer innovations, the utility of statistical graphics for identification of geographic areas with unusually high cancer rates, and an estimate of minority populations.

DIAGNOSTIC RESEARCH - A 1991 estimate of $109,120,000.

Genetic Alterations and Their Clinical Implications

Advances in the field of genetics continue to dominate research in tumor biology and diagnosis. The effort to map the human genome can be expected to have a considerable impact on diagnosis since it will ultimately allow the development of tools to characterize specific gene alterations. Analyses of gene expression and gene alterations are already providing important new information for diagnosis and prognosis.

The ability to predict which early stage breast cancer patients are likely to respond completely to initial treatment and those who will require additional therapy is a major problem. Recent research has shown that the presence of additional copies of an oncogene (cancer-inducing gene) called her-2 (or neu or erbB-2) in the DNA of tumor cells provides better prognostic information than all the other currently used indicators except that of lymph node status. Monoclonal antibody reagents have been developed that can stain biopsy samples in order to assess the level of expression of the her-2 oncogene. Studies are being planned to determine whether there is a correlation between gene expression and response to therapy or the potential of the tumor to spread to other sites (metastasize). Women with early stage breast cancer who have no lymph node involvement will be studied to determine whether it is possible to identify the 25 percent of these women whose disease can be expected to recur based on the expression of this oncogene in their tumor cells.

Disease-free survival of breast cancer patients with no lymph node involvement may also be predicted by the level of expression of another gene known as hsp27. Studies are being conducted to determine the prognostic value of hsp27 expression as well as to understand the mechanisms governing the induction and regulation of this gene.

Genetic analyses of colo-rectal tumors have revealed exciting information about the progression of these tumors from benign adenomatous polyps to carcinomas. Mutations in the ras oncogene were shown to be present in a high percentage of colo-rectal tumors. It has now been demonstrated that these alterations are very early events which can also be detected in benign lesions and perhaps even in nearby areas of the colonic mucosa (the lining of the colon) where tumors are likely to develop but have not yet done so. Further analysis has shown that there are other important chromosomal alterations which occur in colo-rectal tumors that are associated with more aggressive disease. These promising studies are continuing with plans to focus on the clinical correlations between the behavior of tumors and the alterations in the regulation of particular genes.

Other studies indicate that changes in the level of expression of several genes can be used to identify individuals whose colonic mucosa has increased potential to form tumors. These studies will continue to determine which genes are most informative, how sensitive the methods are, and how specific the changes are for predicting development of disease. These findings could assist physicians in determining which patients should be monitored on a more frequent basis for incipient colon cancer.

Examples of the power of gene mapping in the search for specific disease-causing genes include the progress in mapping the region of chromosome 3 involved in renal cell cancer and in small cell lung cancer as well as attempts to locate the region of chromosome 1 that contains the gene for the hereditary form of malignant melanoma. It is likely that the gene for multiple endocrine neoplasia type IIA (MEN-IIA), known to be on chromosome 10, will be located in the near future. Several groups of investigators are planning to test molecular probes for this gene to determine whether the 50 percent of family members who are at risk for developing tumors associated with this disease can be identified.

Research on Tumor-Associated Antigens and Other Markers

Tumor markers continue to be studied for their potential to provide the physician with more information about the nature of the tumor itself. In addition to the study of antigens which are shed into biological fluids, a great deal of emphasis is being placed on developing reagents for histological use. Analyses of other parameters that reflect abnormal cellular behavior, such as the amount of DNA in the cell and the rate of cell growth, are also being pursued.

NCI investigators have developed and are testing a promising new approach for the early diagnosis of lung cancer. This test involves evaluating sputum cell specimens using monoclonal antibodies which react either with antigens of small cell carcinoma of the lung or with antigens of non-small cell carcinoma of the lung. Retrospective studies have demonstrated a high rate of reactions (91 percent) in specimens from patients who developed lung cancer within two years following collection of the specimen. Studies are currently being designed to further evaluate this approach in a prospective clinical trial.

There have been a number of improvements in the use of radio-labeled monoclonal antibodies and antibody fragments in diagnostic imaging during the past several years. One monoclonal antibody, NP-4, has proven to be very useful in detecting tumors in the colon, breast and lung. A method has also been developed to reduce the levels of non-specific binding by labeled antibody in areas that do not contain tumor. This has greatly improved tumor targeting. A number of other studies in nuclear medicine are continuing that should add to the physician's armamentarium by improving the detection of tumors and metastases through diagnostic imaging.

It is very important to develop effective methods to monitor breast cancer patients using serum assays or other non-invasive methods because disease recurrence, even in node-negative breast cancer patients, must be detected. Assays of existing cancer markers such as CEA have been used but are not sufficiently sensitive. Identification of breast-specific markers is needed, and to this end antibodies have been developed that react with antigens of milk fat globules, whole breast cells, cell components or homogenates. A combination of two monoclonal antibodies, DF3 and 115D8, has been developed as a double immunoassay, known as CA15-3. Very recently, a monoclonal antibody has been prepared against purified particles related to the mouse mammary tumor virus found in human breast cancers. The antibody was used to stain sections of human breast biopsies and was positive in 91 percent of primary breast cancers, 100 percent of metastatic breast cancer, and only in two percent of benign tumors, and none of the normal controls. This antibody appears very promising and should be tested further in retrospective studies, since it can be used on paraffin embedded sections.

Monitoring patients with poorly differentiated colon cancers has been a significant problem since these cancers generally do not express the tumor-associated antigens found in well and moderately differentiated tumors. A recent study has led to the development of a monoclonal antibody against surface glycoproteins of poorly differentiated carcinomas. This monoclonal antibody is able to bind to fixed histological sections, and has shown potential as a serum marker for monitoring these colon cancer patients. Further evaluation is planned.

There is considerable evidence that the DNA content of individual cells (ploidy) can be used as a prognostic indicator, with cellular aggressiveness increasing as ploidy increases or decreases from normal levels. For example, the DNA content of breast cancer cells has been shown to have prognostic value. Additional studies, including clinical trials in breast and colon cancer utilizing the resources of the NCI clinical cooperative groups, are being proposed to confirm these findings. These trials will address some of the major questions that remain unanswered about the potential clinical application of these approaches.

Cell proliferation rate, the rate at which new cells are produced, has been a useful indicator of the aggressiveness of breast, colon and other cancers. One approach to the measurement of proliferation has been to monitor the uptake into cells of radioactive thymidine, an essential component of DNA. Because this procedure is complex and time consuming, researchers have looked for simpler and more rapid procedures. Studies are now underway in a number of tumor types to determine the utility of Bromodeoxyuridine (BUdR), a thymidine analogue, as a replacement for the more complex measurements of the thymidine labeling index. Another new reagent that shows considerable promise for determining proliferation rates is the monoclonal antibody Ki-67 which appears to identify proliferating cells.

Emphasis continues to be placed on the transfer of conceptual and technological developments from basic research to the clinic. During the past year, the NCI has formalized a program to assure that promising new diagnostic and prognostic tests will be moved more rapidly into clinical practice. The Diagnosis Decision and Implementation Committee has been formed to assess the status of these tests and to set priorities for large scale clinical evaluations. It is anticipated that two to three diagnostic trials can be initiated in the coming fiscal year.

TREATMENT RESEARCH

Purpose and Method of Operation

Among the important responsibilities of the National Cancer Institute are the discovery and application of new treatments for cancer. An examination of the 1988 SEER statistical survey on cancer incidence and survival in the United States reveals that there has been steady and measurable progress in prolonging survival in patients under 65, particularly in those with tumors affecting the blood forming tissues (leukemias), the immune system (lymphomas), and the reproductive organs (testicular, ovarian, cervical and uterine cancers). However, the common solid tumors that affect patients over 65 have yielded slowly to efforts for improving therapy. Advanced cancers of the lung, colon, breast and prostate cannot generally be cured by present therapies and remain major killers of this segment of the population. The development of new, more effective treatments for these tumors is the major focus of NCI's cancer treatment research.

Advances in cancer treatment research are being made on many fronts. Within NCI's Division of Cancer Treatment, a number of programs are pursuing the development of new, more effective therapies in a variety of complementary ways. The Developmental Therapeutics Program is responsible for the discovery and preclinical development of naturally-occurring and synthetic anticancer and anti-HIV agents. The Biological Response Modifiers Program conducts basic and applied clinical research testing of biological therapeutic agents that may alter host defenses or cancer cells in such a way as to lead to cancer cell destruction. The Radiation Research Program examines unique ways in which electromagnetic energy may be used in the diagnosis and treatment of cancer. Through the Clinical Oncology Program, an entirely intramural program located on the Bethesda campus of NCI, new cancer treatments developed in the laboratory are rapidly applied to patients with cancer, thereby expediting the transfer of knowledge gained in the basic research setting to the clinical setting. The Cancer Therapy Evaluation Program coordinates and monitors the clinical testing of new cancer therapies throughout the United States. Each of these programs contributes in a unique way to the development of new, more effective therapies for the treatment of cancer.

Rationale for the Budget Request

The 1991 budget estimate of $564,223,000 represents an increase of $20,067,000 from the 1990 estimate. The program plans for 1991 are as follows:

PRECLINICAL TREATMENT RESEARCH - A 1991 estimate of $290,759,000.

Drug Discovery - Natural Products Screening Effort

There is a defined rationale behind NCI's effort to focus cancer drug discovery efforts on natural products obtained from plant, marine, and microbial organisms. These life forms survive and grow normally in hostile environments; these organisms produce discrete substances that can regulate their own cellular proliferation and/or can prove toxic to life forms that compete for the same ecological niche. Substances extracted from these organisms possess novel and unique chemical structures quite distinct from those developed through rational drug-design. These active products frequently serve as prototypes from which chemical analogs are made in order to increase antitumor activity.

One example is the isolation of bryostatin from bugula neritina, a seaweed-like animal. This compound, first identified by investigators at Arizona State University under contract with NCI, is particularly interesting because of its broad spectrum of activity in animal tumor models. It also functions as a biological response modifier by enhancing the activity of various immune stimulants such as Interleukins 2 and 4, as well as normal bone marrow colony formation. The patent for bryostatin has recently been licensed to Bristol-Myers and an agreement is currently being negotiated between NCI and Bristol-Myers for the co-development of bryostatin as an antitumor agent. As part of the agreement, Bristol-Myers will pay for the large scale isolation of the compound from the NCI-procured organism and processed extract. This cooperative effort will ensure the timely development of a novel antitumor agent of great interest at little expense to the government. NCI will file the application for the Investigational New Drug (IND) for this agent with the Food and Drug Administration and will sponsor its testing in clinical trials. In addition, Bristol-Myers will pursue the development of other related compounds with potential antitumor activity.

Most anticancer agents currently in clinical use were identified on the basis of their activity against in vivo cancer screens such as mouse leukemia cell lines. In an effort to replace the murine leukemia screening system with a system more relevant to the treatment of human solid tumors, the Institute has developed methods for large scale screening of new compounds against human tumor cell lines derived from lung, colon, melanoma, kidney, ovary, brain cancers, and leukemia. Over the past year, significant progress has been made in the implementation of this screen. The in vitro screening facility at the Frederick Cancer Research Facility became fully operational in the spring of 1989. Beginning in fiscal year 1990, approximately 320 compounds will be screened each week, with an annual goal of 20,000 tests per year.

Drug Development

Once a compound is found to be active in the in vitro cell line screen, efforts to test for in vivo activity begin in parallel with the scale-up synthesis, extraction, or fermentation efforts. The same cell lines used in the in vitro screen are implanted into laboratory mice, where they form tumors in vivo. In this live animal system, the antitumor effects of the new compound can be more thoroughly assessed in terms of drug distribution, metabolism, and excretion. In addition, the compound's toxicity to normal tissue can also be identified through this in vivo phase of testing.

Currently, in vivo antitumor testing is initially accomplished by subcutaneously implanting tumors. Efforts continue to develop "orthotopic" human tumor models, where the tumor is implanted in the anatomical site most closely corresponding to the human tissue of origin for that tumor (i.e., a lung cancer is implanted into the lung of the mouse). The rationale behind this approach is the expectation that the orthotopically implanted tumor will grow and behave biologically more like the original tumor. The orthotopic approach has been successfully utilized to develop in vivo models for lung cancer and will soon be extended to cancers of other organs.

Supercomputer Facilitates Rational Drug Design

In addition to drug screening, another avenue in the development of antitumor drugs is the rational design of active compounds, either by their biological production or chemical synthesis. NCI's supercomputer facility serves as a valuable resource for the investigation and design of numerous potentially effective therapeutic agents by means of its molecular modeling capabilities. The planned upgrade to the current supercomputer facility will provide enhanced capability to further promote these efforts in rational drug design. Through the use of a more powerful supercomputer, researchers will be able to study a variety of larger, more complicated molecular structures. The information derived from such investigations will facilitate the design of newer, more effective anti-cancer drugs. In addition, the multi-drug resistance gene product can be further explored in order to develop inhibitors that interfere with its mechanism of action. These new approaches to drug design will permit researchers to evaluate the potential effectiveness of new compounds more quickly, without the need for lengthy laboratory and clinical procedures. The supercomputer will also be used to explore the three-dimensional folding of proteins based upon analysis of their amino acid sequence. This ability to predict protein conformation should greatly enhance efforts to design both anti-cancer and anti-viral drugs.

National Cooperative Drug Discovery Group Program

As a complement to its drug screening efforts, the NCI supports a broad spectrum of investigator-initiated research in drug design and synthesis. Its National Cooperative Drug Discovery Program (NCDDG) contributes substantially to the development of rational approaches to improving the treatment and cure of cancer. Since its inception in 1983, the NCDDGs have used a multidisciplinary and multi-institutional team approach, drawing from the abilities of the Nation's most talented scientists from academic, non-profit, and commercial organizations in an effort to conceive, create, evaluate, and develop new drugs and treatment strategies for cancer. The scientific approaches are broad and are limited only by the creativity and ability of the members of the group. Active participation by industry is encouraged to allow this segment of the scientific community to contribute its considerable intellectual and material resources.

Harnessing the Immune System to Fight Cancer Using Biological Response Modifiers

Over the past year, research involving biological response modifiers (BRMs) has provided important insights into the relationship between the host immune system and its response to cancer. This involves identification of growth regulating proteins and a better understanding of the role that BRMs play in controlling malignancy. Because of these advances, BRMs are now in every stage of discovery and development, from the important in vitro work aimed at describing new BRMs and understanding their direct and indirect actions (Interleukins 4 and 8, for example), to early phase clinical testing (tumor necrosis factor and gamma interferon), to extensive clinical testing and adoption into clinical oncology practice (Interleukin-2 for malignant melanoma and alpha interferon for hairy cell leukemia and AIDS-related Kaposi's sarcoma). The following describes some of the most promising BRMs currently in the laboratory stage of development:

- **Monocyte/Macrophage Chemoattractant Factor (MCAF):** Investigators within the Biological Response Modifiers Program have cloned a unique family of proteins that activate neutrophils and T-lymphocytes and stimulate a second chemoattractant and activator of monocytes and macrophages (MCAF). These cytokines cause local inflammatory reactions with white blood cell infiltration at sites of injection. Through stimulation of macrophages and other white blood cells, MCAF also has in vitro antitumor activity and may help to augment the host immune response to cancer. Six other members of this new cytokine family have also been identified.

- **Transforming Growth Factor Beta (TGF-Beta):** TGF-beta is an inhibitor of the growth of many cell types. All normal cells which have been examined possess TGF-beta receptors. It has been postulated that the continuous growth of some malignant cells may be due to escape from TGF-beta mediated growth inhibition. In vivo trials with TGF-beta confirm in vitro observations which suggest that it may protect bone marrow from the toxicity of chemotherapy and radiation therapy. Since marrow toxicity frequently limits the dose of chemotherapy that can be safely administered, these results suggest that TGF-beta may be a useful adjunct to high-dose chemotherapy, in addition to its inherent tumor inhibiting activity.

- **Interleukin-1 (IL-1):** NCI scientists have been involved in the discovery and development of this cytokine which is normally produced by monocytes in response to stimulation by foreign proteins (antigens). IL-1 has the ability to protect normal tissues and bone marrow from the toxic effects of radiation. It has also been demonstrated to inhibit the growth of certain types of tumors in vitro. These observations suggest that IL-1 could be of potential value in the management of patients with cancer. It may increase the amount of radiation or chemotherapy that can be safely delivered, thereby increasing the efficacy of therapy, or decreasing the toxicity of currently effective, but toxic, therapy. Future trials will examine the effect of IL-1 on the lining cells of the gastrointestinal tract and on graft-versus-host disease seen in bone marrow transplant patients.

- **Flavone Acetic Acid (FAA):** This agent, originally developed as an anticancer drug, has been found to be more active and potentially useful as a BRM. In cell culture, FAA significantly increases the activity of natural killer (NK) cells which are believed to play an important role in the body's natural defense against cancer. In addition, FAA enhances the antitumor activity of IL-2 in vitro, possibly by increasing the number of IL-2 receptor sites. Each of these effects has significant clinical potential.

- **Levamisole:** Levamisole + 5-FU appears to be the first effective chemotherapeutic regimen capable of reducing the recurrence rate from locally-advanced (Dukes' C) colon cancer (see Clinical Treatment Research). The mechanism of action for this combination, however, is not well understood. Laboratory investigations indicate that levamisole enhances antibody production, restores depressed cellular immune responses, and inhibits suppressor cells. Yet when used alone in the laboratory or in the clinic, it has shown a very limited ability to kill cancer cells. Laboratory and clinical investigation with levamisole has now begun to assess the ways in which it can modify the sensitivity of tumor cells to the toxic effects of cytotoxic chemotherapy and the immune system. These investigations are likely to result in an enhanced understanding of the mechanism by which this biological response modifier mediates tumor cell killing and will allow for the optimal clinical application of this exciting agent.

Antisense RNA and Oligodeoxynucleotides

Over the past two decades, advances in molecular biology have enabled scientists to identify unique characteristics of cancer cells such as the specific gene(s) associated with malignant transformation, and examine how their regulation affects the initiation and growth of cancer. A therapeutic strategy has now been devised to take advantage of the genetic differences between cancer and normal cells through the synthesis of short sequences of nucleotides (the building blocks of DNA and RNA) which are complementary to and therefore bind specifically to the target oncogenes or their RNA messages. These short synthetic nucleotide chains are called "oligonucleotides". This approach has great potential for directing the damaging effects to cancer cells while leaving normal tissues unharmed.

Because of the great promise of these agents in the diagnosis and treatment of many diseases including cancer and AIDS, the NCI has made special efforts to foster further research into the use of these compounds. An international meeting, "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression: Therapeutic Implications," co-sponsored by NCI and industry, was held in June, 1989 at which the latest developments in the field were presented and discussed by 300 scientists from around the world. In addition, NCI's Developmental Therapeutics Program has established a Working Group to monitor and promote the development of new antisense compounds from various sources.

In order to begin the preclinical phase of testing, methods for the synthesis of sufficient quantities of oligodeoxynucleotides at reasonable cost must be further developed. Malignancies associated with or caused by the overexpression of particular oncogenes will be the focus of preclinical and early phase clinical trials of this modality of therapy. Further research will be directed to determine the optimal size and modifications necessary for oligonucleotides to achieve optimal oncogene blockade.

Suppressor Oncogenes in Cancer

The past 10 years have seen a tremendous increase in our understanding of the genetic basis for the development of cancer. Genetic damage leading to malignancy appears to take one of two basic forms: a change leading to increased activity of growth stimulatory forces within the cell via the amplification or activation of dominant cellular oncogenes or the decreased activity or loss of normal growth inhibitory forces due to deletion or inactivation of suppressor oncogenes. The loss of suppressor oncogene activity appears to be responsible for several childhood tumors. Wilms' tumor and retinoblastoma are associated with and indeed may be caused by the inactivation of particular genes. The observation that individuals who survive retinoblastoma or osteosarcoma are at increased risk of developing breast cancer later in life has prompted closer investigation of the role recessive oncogenes play in adult cancers. Over the past year, we have gained important insights into the role of suppressor oncogenes on the development of adult malignancies.

NCI scientists have identified three distinct genetic deletions that are associated with a common adult malignancy -- lung cancer. Loss of a portion of the short arm of chromosome 3 appears to occur in the development of the vast majority of small cell lung cancer cases. This abnormality has been detected in over 95 percent of the small cell lung cancer specimens tested, regardless of whether the sample was taken from a newly diagnosed patient or one who had relapsed. This is clearly the strongest association between small cell lung cancer and any genetic abnormality studied to date. More recently, another chromosomal deletion has been identified in small cell lung cancer: 13q14, the same deletion found in childhood retinoblastoma. But unlike retinoblastoma, in which one inactive gene is inherited, followed by a mutation to the other normal gene, loss of 13q14 gene activity in small cell lung cancers and pulmonary carcinoid tumors appears to be entirely due to somatic mutations that are acquired later in life.

Future research will focus on the specific location and identity of the deleted genes. The precise location of the recessive oncogene on the short arm of chromosome 3 is unknown. Future research efforts will be directed at cloning the recessive gene(s) from this region, identifying their protein products, and characterizing their role in controlling cellular proliferation in normal cells.

CLINICAL TREATMENT RESEARCH - A 1991 estimate of $264,373,000.

Clinical treatment research expands upon the most promising leads developed in the preclinical program and evaluates these new treatments in patients with cancer. The testing of new treatments follows a logical course of progression. Phase I clinical trials establish the maximum tolerated dose, identify the optimal schedule of administration, and provide information on the side effects encountered with the new therapy. Phase II trials examine the efficacy of the new drug in various types of cancer, and Phase III studies compare the new treatment with the best standard therapy to see if the new therapy offers any advantages, in terms of greater activity or reduced toxicity, over the standard therapy.

Adoptive Immunotherapy

Adoptive immunotherapy is a treatment approach in which cells with antitumor reactivity are administered to a tumor-bearing host. These cells then mediate, either directly or indirectly, the regression of established tumor. Since the original NCI report describing the significant antitumor activity of lymphokine activated killer cells with Interleukin-2 (LAK/IL-2), confirmatory clinical trials have helped to define the role of this new treatment modality while laboratory studies have focused on the mechanism(s) by which this approach mediates tumor cell destruction. Clinical trials conducted under NCI auspices have confirmed that there is a 20 to 25 percent response rate for LAK/IL-2 in malignant melanoma and renal cell carcinomas. There has been a concerted effort to try to understand the reasons for the selective activity of adoptive immunotherapy against these two tumors and to improve upon these clinical results. One recent attempt has involved lymphocytes obtained directly from the tumor and grown in cell cultures with high concentrations of IL-2. These so-called tumor infiltrating lymphocytes or TILs have shown 50 to 100 times the cytotoxic activity of LAK cells in cell culture and murine models.

Last year, the results from the first clinical trial of TIL/IL-2/cyclophosphamide were reported. Twenty patients with metastatic malignant melanoma were treated at the NIH Clinical Center with this therapy, 15 of whom had not previously received IL-2, and five whose tumors had progressed despite previous IL-2 therapy. Nine of the 15, or 60 percent who had not previously received IL-2, had objective tumor response and two of the five who had previously been treated with IL-2 responded. The overall response rate for this therapy was 11 of 20 or 55 percent, with one complete remission and 10 partial remissions. Regression was seen in tumor deposits found in the lungs, liver, spleen, bone, lymph nodes, skin, and subcutaneous tissues. This is one of the highest response rates ever observed with systemic treatment of this disease.

It is now clear that reactivity of TIL cells to tumors is dependent upon the high expression of Class II Major Histocompatibility (MHC) antigens; malignant melanoma and renal cell carcinomas characteristically have high levels of MHC expression while most other tumors have low expression of these antigens. Another correlate of response to adoptive immunotherapy has been the in vivo production of other cytokines during treatment. Patients who had the highest levels of tumor necrosis factor (TNF) were more likely to respond to treatment than those with low or undetectable levels. These observations have provided the conceptual underpinnings for the latest clinical trials of adoptive immunotherapy; the use of interferon with TIL cells to increase expression of the major histocompatibility complex.

Gene Transfer Trial of Adoptive Immunotherapy

In an attempt to "activate" TIL cells so that they become even more effective in killing tumor cells, NCI scientists in conjunction with the National Heart, Lung, and Blood Institute have begun the first clinical trial in which a foreign gene is inserted or "transfected" into human cells that are then administered to a patient. This study involves insertion of the gene that confers resistance to the antibiotic neomycin into TIL cells that are grown in culture prior to their infusion. This initial study is examining the feasibility, along with the technical aspects, of the transfer of genetic material into human cells. Preliminary analysis of the first few patients treated has found transfected TIL cells in tumor deposits as early as four days following infusion. These cells remain detectable in tumor tissue for several weeks and in the peripheral blood for up to two months and there does not appear to be any altered or unexpected toxicity attributable to them. Future studies will examine the insertion of additional genes such as those that code for tumor necrosis factor (TNF) or Interleukin-2 (IL-2) into TIL cells in an attempt to further enhance their antitumor activity.

The implications of this study are far-reaching. If new genes can successfully be inserted into human cells, this may provide a new avenue for the treatment a variety of diseases caused by the inactivity or absence of certain genes, such as sickle cell anemia, cystic fibrosis, and alpha-1 antitrypsinase deficiency, among others. The development of "gene therapy" is one of the most promising and exciting frontiers in all of medicine as we enter the 1990s.

Clinical Strategies to Overcome Drug Resistance

Intrinsic or acquired resistance to chemotherapeutic agents stands as one of the greatest obstacles to complete tumor eradication and long-term disease-free survival from cancer. One of the most intensively studied examples of this is the phenomenon known as multidrug resistance. This form of drug resistance is characterized by the development of resistance to a wide variety of structurally and functionally diverse drugs after exposure to any one of them. It is now known that multidrug resistance is caused by the increased expression and overactivity of a drug pump, termed P-170 or p-glycoprotein (pgp) in the cancer cell. A number of common drugs, such as verapamil, quinidine, amiodarone, and phenothiazines, are able to block the function of this pump and result in a reversal of multidrug resistance in laboratory experiments. This observation, coupled with the detection of high levels of P-170 expression in tumors obtained from patients with newly diagnosed colorectal, adrenocortical, or kidney cancers or relapsed multiple myeloma, non-Hodgkin's lymphoma and breast cancer, has led to the first clinical trials combining chemotherapy with pgp blocking agents.

The first prospective trial to attempt this was reported this past year at the NCI-supported Arizona Cancer Center. In this trial, eight patients whose multiple myeloma or non-Hodgkin's lymphoma had become resistant to the effects of VAD (vincristine, adriamycin, and dexamethasone) chemotherapy were retreated with the same regimen plus the pgp reversing agent, verapamil. Three of the eight patients responded to this new regimen, all of whom had overexpression of pgp on their tumor cells. This is the first prospective study to demonstrate that the elevated levels of pgp in drug resistant tumor cells are clinically significant and can be overcome by the concurrent administration of pgp-blocking agents. Two trials using a similar strategy to examine reversal of drug resistance in colon, kidney, and adrenal cancers are being conducted by NCI's Medicine Branch. In April 1989, in order to stimulate more prospective studies of this type, the NCI announced a Request for Applications (RFAs) targeting studies of therapeutic correlates of drug resistance. Thirty-four grant applications have been submitted in response to this announcement, and a number will be funded in fiscal year 1990.

An alternative strategy for overcoming drug resistance is to identify drugs that are not susceptible to the inactivation mechanisms used by drug resistant cells. New anthracyclines have been identified that remain highly toxic for cells that are resistant to doxorubicin by virtue of their P170 glycoprotein. These compounds will proceed to clinical trial in 1990 or 1991. A different strategy for controlling drug resistant cells has been shown from recent work at Memorial Sloan-Kettering, where researchers have found that drug-resistant cells are exceedingly sensitive to the action of certain agents such as HMBA (hexamethylenebisacetamide), which promotes cell differentiation. HMBA has produced clinical evidence of tumor maturation in patients with acute leukemia, and will be tested in drug-resistant patients.

New agents are being developed to overcome the various types of drug resistance. For example, buthionine sulfoximine effectively reduces a cellular detoxification molecule and has recently entered into a Phase I/II clinical trial along with another agent, melphalan, for women with refractory ovarian cancer. Clinical trials of aphidicolin which can repair the cellular damage caused by certain cytotoxins and cisplatin are planned for next year.

Future clinical trials will be designed to determine the nature and prevalence of drug resistance in previously treated and newly diagnosed cancer patients. This information may then be used to select a therapy designed to overcome the mechanisms of resistance detected in the patient's tumor. Other clinical trials will assay for drug resistance at the time of initial diagnosis and at the time of relapse or progression so that a clinical correlation may be drawn between the appearance of drug resistance mechanisms in the tumor cells and the development of clinically drug resistant cancer.

Further research to develop more effective, less toxic pgp antagonists is underway. Cyclosporin appears to block the pgp pump in a manner unlike that of other known pgp antagonists. The pharmaceutical industry has screened a number of cyclosporin analogs and identified agents that not only are more potent pgp blockers than cyclosporin but also lack the undesirable immunosuppressive effects of the parent drug. A new derivative of the drug verapamil is scheduled to enter clinical trials in 1990. It appears to have the pgp-blocking capabilities of the parent drug without its adverse cardiac effects. Other monoclonal antibodies, MRK-16 and MRK-17, which are targeted to the p-glycoprotein and significantly inhibit pump function in vitro have been developed by investigators in Japan. This agent is also expected to enter clinical trial in 1990.

Increased Accrual Into High Priority Clinical Trials

A major impediment to the development of more effective therapies for cancer is the time required to test new therapies. For nearly every malignant disease, crucial studies accrue patients at a rate far below that considered to be desirable, thereby preventing the identification of new effective therapies in a timely and precise fashion. Phase III trials that should take two years to complete accrual may take four to six years or longer. And while the Clinical Cooperative Groups currently enroll about 27,000 patients per year in therapeutic studies, this number must be considered in the context of the one million new cancer cases identified yearly in the United States. For the common adult malignancies, only one-half to three percent of eligible patients are actually enrolled on clinical trials. With so many exciting developments coming out of our basic research laboratories, the clinical application of this new technology is slowed considerably by the limited number of patients entering clinical trials.

Over the past two years, NCI has taken a number of steps to increase patient accrual onto clinical trials. A concerted effort has been made to heighten the public's awareness of clinical trials through newspaper articles and other media as well as to increase the number of subscribers and provide improved access to NCI's clinical trial database, the Physician Data Query (PDQ) system. In fiscal year 1988, NCI identified five "High Priority Clinical Trials" to receive supplemental funding and special emphasis in an attempt to speed completion of these important studies. Protocols for four potentially curable diseases -- locally advanced colon, rectum, and bladder cancers, and advanced stage lymphoma -- were chosen as the trials most likely to provide important new information and to have an impact on national mortality rates.

The campaign to increase physician and patient awareness has already paid off; one of the five trials has completed accrual of patients in less than two years and another is close to completion. The impact of this program has been seen in a 20 percent increase in accrual rates to the High Priority Trials over the corresponding quarter of last year. These improvements have not been limited to these five trials alone; overall accrual onto Phase III protocols is up over 11 percent for the first quarter of 1989 as compared to the same quarter in 1988. Because of the a continued need to enhance patient accrual to clinical trials, an additional six clinical trials have been designated as High Priority Trials; these include trials covering breast, colon, and both small and non-small cell lung cancers.

The outreach program to inform patients and physicians of the benefits of participation in clinical trials is slated for expansion. There are still many physicians who lack sufficient information about clinical trials in order to adequately inform their patients about this option. As part of this effort, a series of videotapes for distribution to physicians and their patients is planned to address this need.

Minorities and Clinical Trials

An important part of improving accrual onto clinical trials will be to increase the representation of minorities enrolled in clinical cancer trials. Currently, minorities are underrepresented in virtually all clinical trials. This is especially ironic since cancer takes a disproportionately high toll on minorities. We need to explore the causes of the high cancer incidence and mortality rates among Black Americans. For many cancers, the incidence and mortality rates for Black Americans are increasing while those for whites are decreasing. For example, between 1973 and 1986, colorectal cancer mortality fell nine percent for whites, but increased by 11 percent in Black Americans. The five-year survival rate from cancer increased for whites from 50.0 percent for those diagnosed between 1974 and 1976 to 52.0 percent for those diagnosed from 1980 to 1985. In contrast, the five-year survival rate decreased for

Black Americans from 38.6 percent to 38.2 percent during the same time periods.

These data clearly show that Black Americans bear a disproportionate health burden from cancer in the United States. In light of these statistics, NCI has launched a coordinated effort to address this issue. The Minority Based Community Clinical Oncology Program (Minority Based CCOP) funded through the cancer prevention and control mechanism is modelled after the successful CCOP program. It is aimed at bringing the latest therapies into minority communities and also increasing minority representation in clinical trials. An RFA issued in 1989 has resulted in eight awards in FY 1990. This program will involve outreach efforts targeted to medically underserved populations in order to provide access to cancer screening and educational programs, and to bring hospitals and medical centers serving minority populations into the clinical trials network. In addition to this effort, the involvement of NCI's Cooperative Group Outreach Program and cancer centers will be essential to the success of enhancing minority access and representation to trials of new cancer therapies. Each cooperative group will be asked to develop a minority-oriented program suitable to its circumstances; both new and existing centers will be targeted.

Adjuvant Therapy of Solid Tumors

The results from recently reported clinical trials indicate that there is an important role for adjuvant therapy in the treatment of several early stage solid tumors. Clinical trials reported during the past year have demonstrated a beneficial effect of adjuvant therapy (in terms of disease-free survival) for women with "node negative" breast cancer (i.e., tumors which have not spread beyond the boundaries of the breast) and for patients with Dukes' C colon cancer (i.e., tumors which have invaded local lymph nodes around the colon). The observed benefit from adjuvant therapy was considerable. For women with node negative early stage breast cancer, adjuvant therapy was associated with a 25 to 48 percent relative reduction in the relapse rate over the first four years of follow-up. For Dukes' C colon cancer, adjuvant therapy resulted in a 32 percent relative improvement in five-year disease-free survival over the group of patients not given additional therapy following surgical removal of all detectable disease. If these treatments were to be applied generally by community oncologists, up to 4,500 more women would avoid a relapse of their breast cancers every year and up to 2,500 more individuals would survive five-years without recurrence of their colon cancer. Thus, the identification and widespread implementation of these treatment approaches constitute key features in the effort to reduce the Nation's cancer mortality rate.

An important aspect of the adjuvant studies in breast cancer is the identification of tumor characteristics associated with prognosis, response to therapy, or the need for an individual patient to undergo adjuvant therapy. More accurate barometers of tumor behavior are needed so that individuals who are at minimal risk for relapse can be spared the toxicity of adjuvant therapy and those who stand the most to gain from additional therapy can receive the optimal treatment. Some potentially useful techniques that may help to distinguish between these two groups of patients include fluorescent antibody cell sorter (FACS) analysis which measures the percentage of cells in the S-phase (i.e., the DNA synthesis stage) of the cell cycle. Another approach has been to look for amplification or overexpression of a certain dominant oncogene known as HER-2/neu in tissue samples. There are now several reports that correlate high HER-2/neu levels in breast and ovarian tumors with a significantly worse prognosis.

A concerted effort is now underway by the cooperative groups to perform such prospective, correlative studies in breast, colo-rectal, and lung cancers. Such collaborative efforts benefit clinical researchers who are in search of more accurate indices to predict patient prognosis and need for adjuvant therapy. In addition, basic researchers who are in need of large quantities of clinical samples from patients with well documented disease and treatment outcome, also benefit from these studies as do the patients themselves who will be able to receive the most appropriate therapy for their cancers.

Suramin

Suramin is a drug that has been used since the early 1920s to treat African river blindness, a parasitic disease known as trypanosomiasis. It became the object of renewed interest in the early 1980s, when it was found to have anti-retroviral activity in cell culture and was tested as a treatment for AIDS. Although its clinical activity against AIDS was minimal, several patients with AIDS-related cancers, such as Kaposi's sarcoma and non-Hodgkin's lymphoma, had a significant reduction in the size of their tumors. These findings prompted NCI researchers to design a Phase I/II clinical trial to ascertain the optimal dose and schedule of administration, the side effects and toxicity, and the antitumor activity of suramin in patients with cancers that were resistant to conventional therapies.

Some of the most exciting results for suramin have been seen recently in men with metastatic prostate cancer. When metastatic prostate cancer no longer responds to hormone therapy, the disease becomes quite difficult to control through the use of chemotherapy or radiation. Preliminary results from the first 40 prostate cancer patients who received this treatment indicate that suramin has definite antitumor activity in this disease. Seven of 14 patients with measurable soft tissue extension of their prostate cancer had objective shrinkage of their tumors. While it is still too early to estimate a definite response rate or duration of response in these patients, this finding is considered important because all of these men had already received hormonal therapy for their metastatic prostate cancer and all had developed progressive disease by the time they began suramin treatment. No other systemic therapy (chemotherapy, immunotherapy) has been known to produce significant responses in this stage of disease.

Larger scale Phase II trials of suramin have recently begun at M.D. Anderson in Houston, Mayo Clinic in Rochester, Minnesota, and Memorial-Sloan Kettering in New York to confirm and expand on these exciting results. Other clinical trials planned for suramin include a Phase III trial comparing the best current hormonal therapy (leuprolide + flutamide) to that same hormonal therapy + suramin for men with newly diagnosed metastatic prostate cancer. There is a special interest in using suramin to treat other growth factor stimulated tumors, as well.

Future research in this area will seek to obtain a greater understanding of the role of growth factors in the development of human cancers. The exact nature of the observed *in vivo* antitumor activity of suramin will need to be studied since this may lead to the development of more active, less toxic agents. Currently available drugs can be screened to see if they possess significant anti-growth factor activity. There is at least one other drug known to fit this description: pentosan. This drug is used extensively as an anticoagulant in Europe. In preliminary laboratory assays, it appears to be more effective than suramin at blocking the activity of growth factors in cancer cells. Another advantage is pentosan's bioavailability; it is effective as an oral preparation, whereas suramin is effective only when given intravenously.

Clinical Trials of Novel Therapeutic Agents: Immunotoxins and Immune Conjugates

Immunotoxins are monoclonal antibodies that have been either chemically or genetically linked to toxic proteins or smaller molecules. Immunotoxins have been synthesized in which monoclonal antibodies are linked to cancer drugs, certain plant or bacterial toxins (such as Ricin, *Pseudomonas exotoxin*, or Diphtheria toxin), or radioisotopes. The monoclonal antibody portion of the molecule guides and brings the toxin to the target cancer cell where the close proximity (in the case of radioisotope conjugates) or internalization of the immunotoxin allows the potent toxic portion of the molecule access to its target(s), disrupting essential cellular processes and resulting in lethal damage to the cancer cell. Some immunotoxins studied so far have demonstrated as much as 10,000 times greater potency over the parent, unarmed monoclonal antibody in cell culture.

Immunotoxins have a variety of potential therapeutic applications. For bone marrow transplantation, they may be used to deplete the harvested bone marrow of donor T-lymphocytes, thereby reducing the risk of graft-versus-host disease in the recipient. Immunotoxins may be infused intravenously to achieve systemic distribution in the treatment of leukemias or disseminated solid malignancies, or they may be used in an intracavitary fashion for tumors that tend to spread within a confined space, such as ovarian cancer or transitional cell carcinoma of the bladder. Since they act in a way completely different than other types of cancer treatment, immunotoxins may be useful adjuncts to surgical, chemotherapeutic or radiotherapeutic approaches in the treatment of cancer.

The pace of clinical development of immunotoxins and immunoconjugates will depend on a number of factors. First, cellular targets consistently expressed in high concentrations by most if not all of the tumor cells will need to be identified. Secondly, since immunotoxins are currently produced using monoclonal antibodies obtained from mice inoculated against human tumors, the host immune response against the mouse antibody portion of the immunotoxin must somehow be controlled or prevented. A preferable alternative to this would be the use of non-immunogenic immunotoxins that are not destroyed by the patient's immune system before they can bind to their target on the cancer cell. Researchers are already developing the technology to achieve this goal including production of human monoclonal antibodies (which are less antigenic than the murine monoclonal antibodies currently used) and the use of recombinant DNA technology to construct a single genetic sequence that contains both the antibody code and the code for a bacterial toxin. This would allow for the production of more homogenous, chemically stable immunotoxins, called genetic "chimeras".

Hematopoietic Colony Stimulating Factors

The human myeloid growth factors have the potential to play a major role in cancer chemotherapy. Preclinical studies have demonstrated that colony stimulating factors (CSFs) support the growth, proliferation, and differentiation of stem cells that produce blood cells both _in vitro_ and _in vivo_. In animal studies, CSFs significantly shorten the time for recovery of bone marrow function following chemotherapy or irradiation and increase the survival of marrow-suppressed animals inoculated with bacteria. Phase II clinical trials reported in the past two years have documented a dose-dependent increase in white blood counts that corrected neutropenia in patients with AIDS and ameliorated treatment-related neutropenia in patients with a variety of solid tumors who had received combination chemotherapy. Two CSFs are currently in large scale Phase II testing: GM-CSF, which predominantly stimulates granulocyte and monocyte production, and G-CSF, which is more specific for the stimulation of granulocytes. Important information to be gained from these studies will include the optimal timing and duration of CSF administration, determination of whether the increase in granulocyte counts correlates with a decrease in the incidence of infections, and determination of whether the incorporation of a CSF into a therapeutic regimen will allow for more dose-intensive, and potentially more effective, chemotherapy to be safely administered.

Proton Beam Therapy

The basic goal of radiation therapy is to kill tumor cells while sparing nearby normal tissue. Interest in the clinical evaluation of proton beams has evolved based on the possibility of achieving superior radiation dose distributions when compared to conventional x-ray therapy. Proton beam radiotherapy has two advantages when compared to x-rays: protons deposit most of their energy near the end of their range, the so-called Bragg peak, and protons have a finite range in contrast to that of x-ray photons. When using proton beam therapy, the Bragg peak may be positioned in the tumor, so that the treatment volume, or the amount of tissue that actually receives the prescribed dose, can be reduced to more closely approach the biological target volume, or the area of tissue containing the tumor itself, along with adjacent areas that also show tumor involvement. Because of the physical characteristics of the proton beam, the surrounding normal tissue receives less radiation damage than would be the case with conventional x-ray therapy. The result of such a reduced treatment volume may be dramatic, particularly if sensitive normal tissues can be protected from receiving any radiation.

Since the mid-1970s, NCI has funded a major program at the Massachusetts General Hospital/Harvard Cyclotron Laboratory (MGH/HCL) for proton therapy. The goal of the MGH/HCL program is to identify tumor sites where the superior dose localization distributions that can be achieved with proton beams yield increased tumor control and/or reduced damage to normal tissues.

The proton beam therapy experience at MGH/HCL is based on the treatment of 1,953 cancer patients and has confirmed the expectation that higher doses to the target volume along with smaller treatment volumes can be used to treat and control selected tumors. Comparing the data to historical controls, proton treatment has resulted in a greater tumor control rate, comparable or lesser morbidity, and no increase in marginal failures. This experience is consistent with the concept that improved radiation dose distribution yields better therapeutic results.

Based on these findings, proton beam therapy appears to have a place in cancer therapy and further research is needed to establish its exact role. There is a need for a small number of state-of-the-art, dedicated, hospital-based proton research and treatment facilities in the U.S. to continue research using this potentially very valuable treatment modality. For this reason, NCI has taken steps to issue a Request for Applications to solicit proposals for exploratory grants that will support appropriate planning and developmental activities in this area. These additional proton beam facilities will perform research to confirm pilot data; improve the delivery of proton beams; determine the optimum proton dose; study additional tumor types; and conduct carefully-designed prospective trials to determine if this radiation modality is superior to conventional therapy with respect to morbidity (complications) and outcome (local control and survival).

Photodynamic Therapy

Photodynamic therapy (PDT) is a new approach to the treatment of cancer which uses light to activate a photosensitizing agent that inflicts selective damage on cancer cells while sparing surrounding normal cells. The concept behind PDT is that certain photosensitizing compounds are retained to a greater extent by cancer cells than they are by normal cells, thereby making them more susceptible to light-induced damage. When exposed to light, the compound damages the cell, probably through a combination of molecular events, including the generation of toxic oxygen radicals and disruption of the microvascular circulation of the tumor.

Because of the need for tumor cells to be accessible to a light source, PDT has been used only in patients with tumors affecting an accessible body cavity or cutaneous surface. Most of this experience has been in patients with bladder, ovarian, and head and neck cancers, obstructing endobronchial tumors, and cutaneous metastases in a variety of malignancies. PDT has shown significant activity in treating endobronchial and cutaneous metastases. Complete responses have been seen in 70 to 80 percent of patients with superficial bladder cancers. In the past year, Phase III randomized clinical trials comparing conventional intravesical chemotherapeutic agents with PDT for this cancer have begun.

Airway obstruction when caused by a tumor is notoriously resistant to conventional treatment. While irradiation may help to shrink the tumor, the lung rarely, if ever, regains function. The shortness of breath that is experienced as a result of this condition remains with a patient until his death. Over the past two years, NCI investigators have applied photodynamic therapy to this group of patients. The early results are quite encouraging: several patients have had a complete re-expansion of their lungs following PDT treatment. These results have led to the creation of larger clinical efforts to define the effectiveness of this therapy in this setting.

Further development of this treatment modality is proceeding on several fronts. New chemical derivatives that are less toxic to normal cells and are not retained in the skin for long periods of time are being developed and tested. New light sources, including an improved laser delivery systems and an injectable chemoluminescent light source, are being developed and may expand the range of applications greatly. (Luciferin, a compound similar to that causing lightening bugs to glow, has the ability to autoluminesce. This property could allow photodynamic treatment of hematologic malignancies, tumors not confined to a body surface or cavity, as well as body cavities not accessible to external light sources, such as the meninges for the treatment of carcinomatous meningitis.) Multi-institutional clinical trials of PDT could help to establish response rates as well as the role of this modality in the treatment of refractory malignancies.

Joint FDA/NCI Fellowship Training Program

The successful development of any new therapy for the treatment of cancer requires carefully coordinated efforts on the part of the Food and Drug Administration (FDA), the National Cancer Institute, and the pharmaceutical sponsor. Individuals involved in this process need to possess a broad array of technical and scientific skills including an extensive knowledge of the diagnosis and management of patients with cancer, an ability to interpret preclinical data and apply that data to the design of clinical trials, an understanding of the methods used in the conduct, monitoring, and analysis of results from clinical trials, and a familiarity with the drug review and approval regulations of the FDA. Currently, no formal program exists to provide such a complete and comprehensive training to individuals interested in careers in the field of drug development and regulation. To this end, the Center for Drug Evaluation and Research of the FDA and the NCI have created a joint fellowship training program in regulatory science. This three-year fellowship will consist of one year of primary clinical responsibility on NCI's adult or pediatric oncology service, followed by two years practical training at NCI's Investigational Drug Branch and the Center for Drug Evaluation of the FDA. Fellows will become involved in the development of selected new agents and will be responsible for coordination and analysis of research data leading to new drug approval. It is anticipated that fellows who complete this training program will be prepared for careers with industry as well as in government. Having individuals with this kind of background involved in the drug regulatory process will likely result in more expeditious development and approval of new cancer therapies. This fellowship also represents the first formal cooperative training effort by the NCI and FDA and will undoubtedly lead to a better understanding and a closer working relationship between the two agencies. Applications to the fellowship program are now being accepted and the first fellows will enter the program in July 1990.

The Children's Inn at NIH

During the past year, considerable progress has been made toward achieving a long-term goal: the establishment of a home for the families of children who are undergoing treatment at the NIH. The Children's Inn is the culmination of efforts by the Congress, industry (Merck and Company which has donated more than $2.5 million for the construction of the Children's Inn), regional developers (Alan I. Kay and Company who oversee the construction of the Inn) and the NIH community. The Children's Inn will be a 34,000 square foot dwelling in a lovely tree-lined setting on the NIH campus. It is ideally located to provide a peaceful and comfortable place for families to stay while their children are receiving treatment at the NIH. It has been designed so that families can attain both privacy as well as the support and comfort from other parents and friends. In addition to its many services, The Children's Inn will contain 36 family rooms. Each room will have two double beds (or, when necessary, a crib) and will have a full bath. There will be common kitchens, playrooms, sitting rooms, game and computer rooms, a library and meeting rooms. Designed by a multidisciplinary team of specialists, The Children's Inn will serve as a model to the Nation and the world of a support facility for children and families undergoing a difficult medical crisis that force them to be displaced from the support of their homes, family and community. The Children's Inn represents the level of accomplishment possible when government, industry, and the private sector cooperate to achieve a common goal.

NUTRITION RESEARCH - A 1991 estimate of $4,056,000.

Cancer cachexia (anorexia and weight loss) is a common problem that affects the quality of life, the response to treatment, and the ultimate survival of patients with cancer. A recent analysis of all clinical trials of forced intravenous feeding documents no discernable benefit of total parenteral nutrition (TPN) in cancer patients. It was recommended that TPN not be used in the management of cancer patients. Current research is focusing on the cause of cancer cachexia in the hope that a better understanding of this problem will result in different strategies to combat it with improved results.

Cachectin/tumor necrosis factor (TNF), Interleukin 1 (IL-1) and gamma-interferon are cytokines produced by macrophages and other cells to combat cancer and infectious processes. Intramural research is focusing on the role of TNF in cancer cachexia. Increased macrophage activity has been associated with elevated circulating levels of TNF in cachectic rats. Tolerance to TNF is being examined as a potential strategy to overcome cachexia. In addition, hormonal therapy with insulin may overcome many of the cachectic effects of cachectin/TNF. Future directions include investigating the roles of other cytokines in cancer cachexia and possibly a clinical trial of insulin therapy in cachectic humans.

REHABILITATION RESEARCH - A 1991 estimate of $4,486,000.

The goal of cancer rehabilitation research is to restore or maintain the patients' fullest physical, psychological, social, vocational, avocational and education potential. Interventions are designed to compensate for, prevent, or minimize long-term or permanent adverse effects of cancer or cancer therapy. Cancer care across the entire course of the disease, including periods when recovery is unlikely, is included. Research on rehabilitation and continuing care addresses the protection and restoration of the physical, psychological, social and vocational functioning of patients, survivors and their families. Research in this program seeks to identify techniques that will overcome barriers to the full utilization of currently available cancer therapies, thereby enhancing the application of state-of-the-art cancer management in the health care delivery system.

Results of clinical trials have had a major impact on reducing the rehabilitation and continuing care needs of cancer patients and improving their quality of life. Research is currently underway in the Community Clinical Oncology Program (CCOP) network specifically comparing the quality of life for different treatment regimens in testicular cancer. Other cancer control clinical trials are examining interventions to reduce the side effects of chemo- and radiation therapy so that patients may receive complete and effective treatment. Studies are being implemented to enhance the ability of breast cancer patients to return to work. Also, through the CCOP mechanism, numerous studies are addressing the most effective regimens for controlling cancer pain and improving the knowledge, attitudes and practice patterns of health care professionals in treating cancer pain.

As cancer treatments continue to improve there is an increasingly large population of adult cancer survivors. An initiative on "Interventions to Improve the Quality of Survival for Recovered Adult Cancer Patients" will be developed in FY 1991. Because of the dearth of baseline information, two phases of research are contemplated: an initial descriptive phase to document problems, and a subsequent intervention phase. The choice of survivor groups targeted for study will be influenced by the public health impact (people who are expected to have a significant portion of their working life ahead of them), and by the possibility of experiencing serious long-term treatment sequelae.

Research on the needs of cancer patients who are living at home and the adequacy of services received has produced important findings. An RFA will be released in FY 1991 to test interventions to relieve major problems in current care of cancer patients living at home.

CANCER BIOLOGY

Purpose and Method of Operation

Cancer biology supports basic research focused on understanding the nature of the tumor cell, its intrinsic biological properties that promote unrestrained growth and are responsible for the ability to invade and metastasize, its influence on the local environment and its interaction with normal host immune defense mechanisms. This investment in basic research is the key to developing more accurate cancer diagnosis and will provide the rationale for useful cancer therapeutics and prevention strategies of the future.

By utilizing state-of-the-art technology and new design strategies, a genetic basis for cancer is now emerging that is a major emphasis of research to complement and enhance our understanding of the molecular biology of tumor cells. Both dominant oncogenes which, when activated, exert a positive inductive influence on cancer cell growth, and recessive suppressor genes which function to inhibit the growth of cancer cells have been identified as being involved in the malignant behavior of tumor cells. These genes are responsible for production of proteins that serve a variety of biological roles: involvement in the transfer of information from the external environment into and throughout the cell, control of the expression of new cell products characteristic of a tumor cell and important in its aggressive behavior, or as functional cellular proteins themselves such as enzymes. However, expression of any of these types of genes is in itself insufficient to explain human cancer. The interaction of the tumor with its host involves all of the systems of the body, but none is more important for its potential to control tumor growth than the immune system. Research has continued to unravel the enormous complexity of molecules and cell types that make up the immune system and are involved in combating tumor growth. Advances in transplantation of immune system cells and manipulation of their specificity promise to aid in cancer treatment. Identification of the molecules that control immune cell homing to sites of tumor growth may lead to improvements in the ability of the immune system to reach and attack solid tumors. Cancer biology will continue to use the methods of biochemistry, molecular biology and immunology to better understand the process of tumor growth and metastasis and to produce a new generation of strategies for the diagnosis and therapy of cancer.

Rationale for the Budget Request

The 1991 budget estimate of $301,826,000 represents an increase of $15,118,000 from the 1990 estimate. The program plans for 1991 are as follows:

IMMUNOLOGY - A 1991 estimate of $113,380,000.

The T-Cell Receptor for Antigens

Lymphocytes are distinguished by their exquisite antigen specificity. In B cells, this specificity resides in antibodies, which have been studied for many years. In T cells, the specificity is due to a similar but distinct set of cell surface molecules generally referred to as T-cell receptors (TCRs). Studies on T-cell receptors are important for the analysis of T-cell leukemias and for understanding normal T-cell development. Most effective immune responses to tumors involve T cells, so an understanding of how T cells work is crucial to improving the immune response to human cancer. TCRs evaded detection until recently, but the rate of progress in understanding these molecules and the genes that encode them has been explosive in the last few years, with no sign of slowing down. The first TCR to be recognized was called alpha beta and was shown to be present on most mature, circulating T cells. More recently, a second type of TCR, called gamma delta, has been shown to be present on a smaller number of T cells. The relationship between alpha beta-expressing T cells and gamma delta-expressing T cells has been studied intensively this year. It has been shown that gamma delta T cells are expressed earlier in fetal life than alpha beta T cells and that these subsets are distinct from one another, evolving separately throughout life. While alpha beta T cells become numerically dominant in adult life, gamma delta T cells continue to play an important role.

Studies are underway to clarify the respective roles of alpha beta and gamma delta TCR-bearing T cells, particularly in the immune response to tumors. Questions exist over the number, distribution and surface phenotype of gamma delta T cells and research will focus on resolving these issues. The capabilities of gamma delta T cells for tumor cytotoxicity and for antigen-specific recognition in general will be assessed first by looking at a wide range of _in vivo_ responses and determining the T cell type responding under normal circumstances. As it becomes clear what factors predispose to a response by gamma delta T cells, this type of response will be induced specifically by appropriate stimulation _in vivo_ or _in vitro_ to assess the maximum possible usefulness of gamma delta T cells in optimizing an anti-tumor response.

Transplantation: Induction of Tolerance

Transplantation of tissues and organs has enormous potential for the treatment of human diseases, including cancer. Bone marrow transplantation has become the treatment of choice in some areas of leukemia and lymphoma and holds great promise for immune reconstitution following therapy for solid tumors. To date, the vast majority of clinical transplants have been performed using non-specific immunosuppressive drugs to prevent rejection. However, when one suppresses the immune response sufficiently to prevent transplant rejection, one also diminishes the patient's ability to respond to pathogenic organisms. The major complication of such treatment has therefore been infections. An additional complication of bone marrow transplantation is the potential development of an immune response of the donor cells against foreign components of host tissues (Graft versus Host Disease, GVHD). Because

GVHD is caused by mature T cells in the donor marrow, monoclonal antibodies have been used to deplete these T cells prior to bone marrow transplantation. Although this procedure does result in a decrease in GVHD, a significant delay in immunologic reconstitution and an increased incidence of relapse in patients with leukemia has been observed.

The induction of specific immunologic tolerance, on the other hand, involves elimination of only the immune response toward the grafted tissue or organ, without impairing the immune response to pathogens. It was shown many years ago that this phenomenon could be induced in neonatal animals by the injection of bone marrow cells from another donor within the first 24 hours of life. The principles derived from these studies will provide new and valuable insights into the complex phenomenon of immunologic tolerance.

Recent studies in experimental animal models have been directed toward the induction of specific transplantation tolerance in adult animals in order to permit transplants to be accepted without the need for the continuous administration of immunosuppressive drugs. Using a combination of irradiation and monoclonal antibodies, the recipient's immune system is depleted, and then bone marrow from a suitable donor is mixed with bone marrow harvested from the recipient before irradiation, and both are injected. As new lymphoid and hematopoietic (blood-forming) cells develop in the recipient, they appear to induce mutual tolerance, without requiring any further immunosuppression. The resulting "mixed chimeras" have been found to be specifically tolerant to transplanted tissues from the bone marrow donor, and yet to have excellent immune responses to all other antigens tested.

Further development of these findings and application to humans has great potential importance in transplantation because the induction of specific tolerance could permit long-term acceptance of transplants even between individuals differing by many transplantation antigens. This would avoid the need for matching donor and recipient. In the case of bone marrow transplants for leukemia, a modification of this procedure would make this treatment available to the more than 50 percent of patients who do not have a matched sibling for a donor.

Pluripotent Stem Cells

All of the cells that make up the immune system originate from a population of bone marrow cells called pluripotent stem cells. These cells are self-perpetuating, and produce progeny that can differentiate into all of the different subsets of cells that make up the hematopoietic (blood forming) system. Theoretically, the progeny of a single pluripotent stem cell are capable of repopulating all the hematopoietic cell lineages. The existence of such pluripotent stem cells is well accepted, although the evidence is indirect. Because the dose-limiting toxicity of many chemotherapy regimens is measured by the effect on bone marrow stem cells, protecting such cells from damage and maximizing the rate at which they can repopulate mature immune cell subsets is a major goal of cancer therapy research.

Important progress on stem cells has recently been reported by a number of laboratories. Stem cells have been obtained from mouse bone marrow in sufficient purity to allow some characterization of their morphology and surface phenotype. By their nature, stem cells lack the surface molecules found on functionally mature cell subsets. This has made purification largely a negative process of eliminating the more mature cells from a starting population of bone marrow cells. Now, a few useful positive markers for stem cells have been identified which greatly facilitates this work. Very recently, there have been studies on human bone marrow which show that the lessons learned from mouse stem cells are applicable to the technically more difficult problem of isolating human stem cells.

As stem cell purification and characterization proceed in both human and mouse cell lines, research findings will be applied to the goal of optimizing tumor therapy. Purifying stem cells is potentially beneficial to cancer patients in two ways. First, if the patient has functional, nonmalignant stem cells, these cells could be isolated, preserved and used to reconstitute the cancer patient's immune system after therapy is used to eradicate all tumor cells in the body. Second, the use of purified stem cells for bone marrow transplants offers an alternative to tolerance induction (see above) to reduce the risks and improve the usefulness of bone marrow transplantation as a treatment for cancer. In favorable cases, it may be possible to give a patient stem cells from a related or unrelated donor instead of using those from the patient. The use of stem cells, instead of intact bone marrow, would eliminate the most serious side effect of bone marrow transplantation, Graft versus Host Disease, which is caused by the mature T cells in the transferred marrow population attacking the cells of the host. Very exciting models of foreign transplantation have recently been developed involving the transfer of human stem cells into an immunodeficient mouse. These models hold great promise for basic research on the immune response to tumors, drug testing and vaccine development, and research in this area will be emphasized.

A related area of intense interest is growth stimulation of primitive stem cells. A major difficulty of bone marrow transplantation is the time required for hematopoietic cells to engraft and develop the functional capability to prevent infection in the patient. A number of growth factors, including interleukin 1, interleukin 3 and the three known colony stimulating factors (G-CSF, M-CSF and GM-CSF), are known to be required for immune reconstitution. To promote rapid hematopoietic reconstitution, optimal levels of these factors must be given with stem cells. A variety of doses are being tested in many experimental and clinical situations in patients, experimental animals and cell culture systems. The active sites of these molecules are being studied, and it is likely that additional growth factors remain to be discovered. This is a major focus of work in the coming year.

T-Cell Suppression

The immune system is regulated both positively and negatively at many different points. It is just as important to be able to shut off an immune response when it has done its work as to be able to turn it on in the first place. A wealth of functional studies over many years have shown that T cells are frequently involved in actively suppressing ongoing immune responses. Indeed, T-cell suppression is a frequent observation in the immune response to tumors. CD4+ T cells have been divided into subtypes based upon their expression of different surface markers. Recent studies have suggested that unstimulated CD4+ T cells can only deliver a suppressive signal to other lymphocytes. Upon stimulation, however, there is a reduction in the expression of one surface marker while the expression of the other is increased. In this more mature state, the specificity of the cell remains the same, but the type of signal delivered changes from suppression to that of helper. Thus, suppression may be a property not of a separate lineage of T cells but may represent a particular developmental stage. These studies are important for understanding the mechanism of suppression in order to control it in cases where it appears counterproductive, such as in the immune response to a tumor.

Because T-cell suppression has been such a difficult area of investigation for so long, it will be necessary to proceed very deliberately in evaluating the exciting new hypotheses that have been advanced to explain it. Suppression can occur at many levels in the immune system and it is unlikely that any single mechanism involving any one cell type will be sufficient to explain all of the observations. An important place to start will be with a detailed assessment of fresh CD4+ T cells that express different surface markers. Because these cells do not suppress directly, it will be necessary to identify their target -- the cell that they can trigger to be directly suppressive. It is likely that both cell-cell contact and the secretion of soluble factors play a role in the generation of suppression. The involvement of known lymphokines and known cell-surface molecules will be assessed using specific monoclonal antibodies to inhibit either suppression or its generation. The ultimate goal is to prevent premature termination of a potentially useful immune response against a tumor. Before strategies can be developed to make this happen, the biology and biochemistry of suppression must be more fully understood.

Adhesion Molecules and Lymphocyte Homing

Lymphocytes are often thought of as completely solitary cells because, unlike most cells, when circulating in the blood they have no long-term interactions with other cells. Thus, while there has been interest for many years in the adhesion molecules that hold the cells in organized tissues together, these molecules were not sought on lymphocytes. Recently, however, it has been realized that adhesion molecules of at least three types are crucial to the functioning of the immune system. Examples of each type of molecule have been identified, but only within the past year have their interrelationships been clarified. Known molecules have been cloned, homologies established and new molecules identified.

The first type of adhesion molecule permits interaction with connective tissue components such as collagen, laminin and fibronectin. These molecules, known as the VLA family, are presumably important for immune cells that leave the blood and migrate through tissue spaces to reach areas where tumor cells are growing to kill them. Their ability to reach their target is controlled in large part by their expression of adhesion molecules of the VLA type. Studies of these molecules may improve our ability to target immune cells to solid tumors.

The second type of adhesion molecule is the one most specific for the immune system. These molecules make lymphocytes and other white blood cells stick together well enough to exchange signals of various types. The "stickiness" is nonspecific but it facilitates more specific binding. Cytotoxic T cells, for example, recognize their specific targets using the T-cell antigen receptor. There are, however, not enough of these receptors to hold the T cell to its target long enough for killing to occur. Nonspecific adhesion molecules on the killer and target combine to make killing possible. The nonspecific adhesion molecules are diverse in structure. The most widely distributed of the group, LFA-1, has been the subject of the most recent work. For example, the expression of one of its ligands on melanoma cells has been shown to correlate with an increased risk of metastasis. Interestingly, this ligand has also been shown to be the cell surface receptor for the virus that causes the common cold.

The third type of adhesion molecule in which recent progress has been made are the lymphocyte homing molecules. Homing molecules offer the broadest opportunity for future investigation because so little is known about their functions. Lymphocytes traffic through the blood to specific, preprogrammed vascular beds, where they exit the circulation and enter the lymphatic system. Some lymphocytes are programmed to home to lymph nodes, other to gut-associated lymphoid tissue. A major focus of research will be the study of homing to sites other than the lymph nodes and gut. It is likely that there are other sites of preprogrammed lymphocyte traffic and that these destinations are genetically determined by the expression of homing molecules related to those identified to date. In recent years, a number of cell-surface molecules have emerged as candidate homing receptor molecules. Genes for several of these molecules have been cloned and sequenced very recently and a coherent picture of their interactions has finally begun to emerge. The first molecule associated convincingly with homing was that recognized by the monoclonal antibody MEL-14; this molecule has been sequenced this year.

A more important issue for cancer is lymphocyte homing not only to specific lymphoid organs but to sites of inflammation or tumor growth. Lymphocytes are drawn from great distances to such sites by soluble attraction factors, but once they arrive, they leave the circulation by binding to temporary homing sites induced in the wall of the blood vessel by the inflammatory process. Research will focus on the contributions of interleukin-1 and tumor necrosis factor in this type of homing, along with those of other inflammatory molecules.

Improved Cytotoxicity Against Tumor Cells

The introduction of cellular adoptive immunotherapy for cancer, using lymphokine-activated killer cells (LAK) and tumor-infiltrating lymphocytes (TIL), has been an important advance in several forms of cancer. In order to make improvements in cellular immune therapies, several important basic questions must be answered. LAK cells have now been shown to derive in large measure from natural killer (NK) cells in the blood. It is important to know how LAK and NK cells recognize tumors and kill them. Natural immunity, which includes NK and LAK and several other components, differs from T-cell immunity in that it is operative without prior exposure to antigen and thus can react immediately. The NK cell has been shown to have many different activities in vitro and is postulated to have a variety of functions in vivo as well. However, it has been difficult to characterize satisfactorily because it is not known how it recognizes its target. A single clone of NK cells can kill a wide variety of tumor cells and virus-infected cells, as well as certain normal cells. Without knowing what molecular interactions trigger recognition and killing, there has been no systematic way of exploiting or improving the ability of NK and LAK cells to kill tumor cells. After years of searching, there are now several NK-specific cell-surface molecules that have been identified and shown to be important for cytotoxicity. Antibodies to these molecules block killing. In one case, an apparently complementary target cell molecule has been described. NCI-supported scientists are focusing on characterization of these molecules to establish their functional roles.

Immunologists have been aware for many years that various immune cells can infiltrate into tumors, but which types of cells actually contribute effectively to the eradication of a solid tumor are still unknown. Immune cells have been recovered from tumors grown in culture with interleukin-2, and shown to have the ability to kill tumor cells in vitro and to cause tumors to regress when injected back into animals or patients. These tumor-infiltrating lymphocytes (TILs) are now known to be a type of cytotoxic T cells and this type of immunotherapy is being tested clinically. In spite of the intense clinical interest, little is known about the spectrum of cells which are recruited to the site of a progressing tumor during the natural evolution of the malignancy. Given what is known about the role of suppression of the immune system, it is necessary to study the natural immunobiology of solid tumors throughout the course of the development, growth and potential metastatic dissemination of the tumor.

However, studies of the natural immunobiology of solid tumors cannot be done readily in man. When detectable by a physician or patient, tumors have progressed beyond the point where the immune system is capable of controlling growth unaided by therapeutic stimulation. Thus, these studies require appropriate animal models in which the development of tumors is predictable and the tumor systems are analogous to human cancers. Few such systems currently exist. The development of immunodeficient mice which can be reconstituted with human immune cells has created the potential to study the human immune response to human tumor transplants. Also, transgenic mice are becoming available which have a high incidence of spontaneous tumor development. Research will focus on studies of the naturally occurring immune response to solid tumors to better understand the circumstances contributing to the success or failure of immunologic control of tumor cell growth. The development of appropriate models for the study of immunologic aspects of the major solid tumors will be emphasized.

TUMOR BIOLOGY - A 1991 estimate of $188,446,000.

Genetics of Cancer

Research into the genetic basis of cancer continues to produce advances in identifying the changes in genetic information which characterize specific cancers and in revealing the contribution these alterations have to the ability of tumors to grow and metastasize. Systematic analysis of the severity and types of genetic changes detected in human tumor tissue may provide useful molecular correlates predictive of tumor behavior. Such analyses may also help to explain the heterogeneity of tumors regarding responses to chemotherapy. New strategies of molecular genetics will also be employed to focus on single steps in this process to attempt to understand what kind of pathogenic events are taking place in the cell that allow segments of chromosomes to be irreversibly deleted from or re-arranged in the cell's genome.

In some tumors, the loss of the activity of a single gene strongly correlates with the uncontrolled growth which is typical of cancer cells. Such genes are called "suppressor genes", because their role in normal cells is to keep growth in check. The most notable example of a suppressor gene is called RB, which is associated with the retinoblastoma tumor. Identification of the RB gene is considered a significant break-through in tumor biology and has stimulated the search for other genes that are members of this new class of cancer genes. They will be important tools for genetic manipulations of cells and animals which will in the next several years be able to explain growth control mechanisms at a molecular level. Probes that can detect the loss of RB or other tumor suppressing genes will be useful in identifying genetic predisposition to cancer. If a relationship can be shown between a single suppressor gene and a sub-group of malignancies, useful new pathology classifications may result. Finally the potent growth-suppressing activity of the RB protein suggests that it may provide a new approach to future cancer treatment based on precise knowledge of its cellular function.

Frequently the genetic alterations observed in cancer cells are much more subtle than the total loss of the DNA which encodes a specific gene. These subtle changes relate to the way in which a cell chooses which genes are to be used or expressed, at any given time or under a given set of external conditions. Gene expression is controlled through the interaction of cell-specific proteins with DNA sequences, called enhancer elements, near the gene itself. Much recent research has focused on the location, structure, number, and specificity of cell-specific enhancer elements. Because of their variety, enhancer elements and the proteins which bind to them offer substantial promise for intervention in tumor cell processes without harming normal cells. The newest research has shown that several regulatory proteins may form a complex with each other before binding to their target enhancer element, and research to determine the order in which these specific proteins bind to the enhancer or to each other as another level of genetic regulation should soon be very productive. Future research into the regulation of cell-specific gene expression should reveal those components which could be exploited to confine a tumor to the organ in which it arises or to inhibit the ability of a metastatic cell to establish itself in a new location.

Another regulatory mechanism which is less well described is that of "activation" or "extinction". Normal cells have properties of the specialized tissues which they comprise. These properties are maintained through two opposing mechanisms: one which activates the expression of genes required for the specialized functions of the cells of a particular tissue and the other which extinguishes the expression of genes which confer specialized functions of the cells of a different tissue. In many instances tumor cells have lost their previous specialized functions, possibly due to loss of the factors that confer tissue-specific activator or extinguisher activity. Finding ways to restore normal tissue-specific regulation, by either activating appropriate genes or repressing inappropriate genes may be the means to return the tumor tissue to its normal pre-neoplastic state. Now that the chromosomal locations of the genes for certain of these factors are known, sufficient quantities of the factors themselves should finally become available to explore the mechanism of this precise biological system. Information acquired on the molecular signaling involved in specifying the characteristics of a normal cell type should also begin to explain the loss of these characteristics in tumor cells. If activators and extinguishers are mediators of genetic regulation, then the DNA sequences at which they usually act may simply be deleted or rearranged in tumor cells. If the control is at the level of protein synthesis it is more likely that the factors themselves are abnormal.

Metastasis Biology

Tumor invasion and metastasis is the major cause of cancer treatment failure. There is a great clinical need to develop new methods to predict the aggressiveness of an individual patient's tumors, to identify clinically occult metastases, to successfully treat locally invasive cancer, and to eradicate established metastatic colonies. In order to provide a rational basis for developing clinical strategies, a major emphasis has been placed on studying the gene products involved in tumor invasion and metastasis. Investigators at the NCI have identified and characterized a set of gene products which may play a role in the regulation of invasion and metastasis: laminin receptor, autocrine motility factor, NM23 metastasis suppressor protein, type IV collagenase, and TIMP-2 metalloproteinase inhibitor. It is currently thought that these metastasis-associated gene products may be different from those which regulate tumor growth, which is in keeping with the concept that benign tumors may grow in an unrestrained fashion, but fail to invade.

The first step in tumor cell invasion is attachment of the tumor cell to proteins, such as laminin, in the membrane surrounding the normal tissue. Augmented levels of laminin receptor are associated with certain aggressive human cancers such as colon and breast cancer; thus the identification of elevated levels of laminin receptors may be a valuable adjunct in the diagnostic evaluation and prognostic prediction of these cancers. Antibodies have been developed against the binding domain of the laminin receptor, and these antibodies have been used to target cancer drugs. This approach has been shown to be very effective in killing human breast cancer cells in experimental systems.

The autocrine motility factor (AMF), a growth factor which is secreted by tumor cells, binds tightly to a tumor cell receptor, and profoundly stimulates locomotion. Preliminary clinical studies have shown a positive correlation between elevated urine levels of AMF and increased aggressiveness of human bladder cancer. The pathway through which AMF exerts its effects on tumor cell motility has been identified, and a specific inhibitor of this pathway has been identified which arrests tumor cell motility and adhesion, and can prevent the formation of new metastases and inhibit the growth of established metastases in animal models. This compound has been approved for phase I clinical trials at the NCI.

A new gene, NM23, has been identified that appears to be a natural cellular suppressor gene; its normal function being to prevent the changes that result in malignant growth. During the past year, this the human NM23 gene has been cloned and the previously unknown protein product of the gene has now been identified. A surprising discovery has been that the human NM23 protein has been conserved over millions of years of evolution, suggesting that it serves a vital function in the cell. Reduction or mutation of NM23 have been shown to correlate significantly with the metastatic aggressiveness of certain human cancers; high NM23 levels are associated with a favorable prognosis. The NM23 protein is being produced in large quantities by recombinant DNA techniques, which should enable scientists to more fully explore its therapeutic potential.

Type IV collagen, which is genetically different from other types of collagen (connective tissue), forms the structural backbone of the membrane surrounding normal tissue. Type IV collagenase is an enzyme, secreted in large amounts by tumor cells, which can specifically degrade type IV collagen. Increased levels of type IV collagenase are strongly correlated with increased aggressiveness of human bladder, gastric, and colon cancers. The functional subunits of the enzyme have recently been identified, suggesting possible strategies for the design of a enzyme inhibitors. Of particular importance has been the discovery of a novel inhibitor protein, TIMP-2, which binds to type IV collagenase as well as other enzymes thought to be important in malignancy and blocks metastasis formation in experimental models. New studies suggest that TIMP-2 may also inhibit the formation of new blood vessels (angiogenesis), a process that is critical for the development of malignancy. This novel human metalloproteinase inhibitor may function as a cancer suppressor gene product since a cancer cell can make both type IV collagenase and the inhibitor protein. TIMP-2 is being synthesized by recombinant DNA technology for experimental therapy trials.

Angiogenesis is a critical and limiting step in tumor progression. Investigations on how endothelial cells are attracted to tumor cells and how they are activated to form new capillary cells will continue to be a primary focus of research in angiogenesis. Further, it is essential to understand how normal cells suppress this process and to identify both the genes and protein products involved. Further exploration of the protein product of one suppressor gene which seems related to angiogenesis will be a priority. The development of new inhibitors of blood vessel formation that can be used in patient therapy should also be useful in management of a variety of diseases, including cancer.

Transgenic mice have become an indispensable tool in efforts to dissect the critical steps of tumor progression. They now have an established role in defining the process between hyperplastic growth and angiogenesis which precedes overt tumor formation. Progress in cancer research has frequently been inhibited by the complexity of the disease; in the past, metastasis had to be studied largely as a problem of cell-to-cell interaction and progress depended on the rate of progress in cell biology. The clear definition of steps in this model system and the access they provide to real genetic analysis offers the possibility of identifying the factors and expressed or repressed genes responsible for malignant growth.

Tissue Interactions in the Development of Malignancy

Tissues are complex networks of different cell types and a supporting extracellular matrix. It has become increasingly clear that this matrix and the so-called stromal cells which synthesize and help fabricate it are distinctive within each organ type just as the epithelium in each organ is unique. Since solid tumors are responsible for the majority of cancer deaths each year, investigations have increasingly focused on the role of the stromal cells and the matrix and how they might contribute to the malignant behavior of these carcinomas. As malignant tumors progress in the breast and prostate, they lose the responsiveness to the sex steroids that is so critical to growth and differentiation in the normal glands. Increasingly it has been shown that the stromal cells in these organs may also be steroid hormone-responsive and further that they synthesize and secrete growth factors into their environment in response to steroids and other hormones. Whether or not they also become hormone resistant is not known.

It has been demonstrated in several experimental systems that the effect of stroma on the epithelium is profound. When breast epithelial cells are grown in vitro, the degree of growth and differentiation and milk protein synthesis depends on the composition of the culture matrix. A chimeric tissue constructed from rat normal stromal cells and prostate adenocarcinoma, transplanted into a host rat will mature into a pseudo-normal prostate gland. Understanding the mechanism of this cell-cell communication and interaction may reveal how cancer cells avoid the growth constraints and control signals to which normal cells must respond.

Considerably more research will be needed to define the various stimulatory and inhibiting factors secreted by the different cells in a tissue, and to determine their target cells and the mechanisms whereby they have their effects. In prostate cancer, paracrine factors secreted by stromal cells are very important for the growth of androgen-insensitive prostate tumor cells. What these factors are and whether they act to stimulate the tumor cells to secrete their own autocrine growth factors or if they act directly as growth factors is not yet known. This research also suggests new avenues of inquiry into the mechanism of development of hormone-independent carcinomas.

A new idea in hormone-dependency of breast cancer was recently posed when it was observed that a variant form of a gene which codes for estrogen receptor protein occurs in some women with breast cancer who also had a history of miscarriage. This aberrant gene is associated with diminished estrogen receptor content and suggests that there may be an association between lower estrogen levels within breast cells and cancer. As receptor levels constitute an important prognostic factor in patient selection for hormone therapy in breast cancer, the presence of this variant gene may suggest more appropriate therapies. More studies will be conducted to explore the differences between the normal and variant receptor structures.

Supercomputer

The National Cancer Institute's supercomputer facility is a high-speed computing center located at the Frederick Cancer Research Facility (FCRF) in Frederick, Maryland. This computational resource, organizationally known as the Advanced Scientific Computing Laboratory (ASCL), has been operational for about three years. During this time, it has provided high-speed computing support to the scientists of NCI, NIH and the Department of Health and Human Services, as well as to researchers from leading educational institutions throughout the United States. Communications with the entire NIH scientific community have been enhanced with the connection of a very high-speed communication line to the Bethesda campus. This high-speed line permits easy access to the Cray supercomputer by NIH and NCI scientists on the main campus. Connections to the National Library of Medicine and the University of Maryland provide nationwide access to such important scientific networks as ARPANET, NSFNET, and BITNET. Users can gain access to the network through their local universities. Scientists at Johns Hopkins University, the Mount Sinai School of Medicine in New York City, and Cornell University are regular users of the supercomputer, as are scientists from leading educational institutions around the country.

The resources provided by the ASCL include personal computers, graphics workstations, large minicomputers, and the Cray X-MP/24 supercomputer. There are currently more than 400 registered users of the computational resources provided by the ASCL. At present, the Cray is averaging nearly 5,000 jobs per month and 4.9 million cpu seconds of processor time. The processors are yielding a very impressive 85 percent utilization rate.

In the relatively short time the ASCL has been operational, the success of applying modern supercomputer methods to biomedical science has become apparent. The Cray X-MP/24 currently in use is already playing a major role as a instrument for basic biomedical research, in structure analysis of drugs and macromolecules, in the analysis of gene sequences of genes of humans and viruses, and in a variety of new areas of biomedical science.

The science being supported at the Center encompasses a wide array of disciplines in biomedical research. Computational projects are being actively pursued in the areas of x-ray crystallography of viral proteases, molecular modeling of membrane proteins and HIV protease, DNA structure, sequence analysis prediction of RNA secondary structure, and protein spectroscopy, to name a few. Scientists engaged in structure-function studies of important compounds are relying heavily upon the molecular modeling capabilities offered at the ASCL. High resolution NMR spectroscopy is enabling researchers to elucidate structural details of proteins and oligonucleotides in solution, and the supercomputer is being utilized for calculations using this new and powerful technique. As the database of human genomic sequences grows, it becomes increasingly important to extract and understand the information encoded in it. In addition, computation techniques are allowing the direct determination of structures without the need for multiple crystallographic studies. While these techniques have been known for some time, they could not be must effectively applied until the advent of supercomputers.

These are only a few of the ways that the high-speed computational methods employed at the ASCL are facilitating the development of solutions to problems in basic biology, molecular genetics, and therapy. It is important to note that, by their own subjective estimates, scientists have reported a six- to ten-fold increase in their productivity by using the supercomputer. Improvements of this magnitude in an investigator's capability must be considered significant and may be viewed as another important benefit of the facility.

Because there is every reason to expect that major growth in the computational needs of cancer biology and clinical cancer research will continue, the Congress provided funds in FY 1990 to purchase a machine with additional processors and vastly increased memory capability. The acquisition process for this upgrade was conducted last year; and the new, upgraded facility will be available to users sometime during FY 1991. This upgrade also included provision for major innovative computational resources, such as massively parallel architectures and special purpose processors.

While the ASCL's success to date in applying supercomputer technology to the basic sciences has been impressive, the new upgrade will allow novel approaches to problems that are too large and complicated for the current machine. These include the investigation and design of more efficient anti-cancer drugs, prediction of the structure of the entire AIDS virus genome, the use of new crystallographic techniques and nuclear magnetic resonance to study oncogenes and viral proteins, and the direct prediction of protein folding from amino acid sequences.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Resource Development

Authorization: Indefinite

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
PROGRAM ACTIVITY:						
Cancer centers support	12	$104,429,000	17	$104,588,000	+5	+$159,000
Research manpower development..........	29	49,733,000	29	49,879,000	--	+146,000
Construction..........	3	5,165,000	3	1,645,000	--	-3,520,000
Total..................	44	159,327,000	49	156,112,000	+5	-3,215,000

MECHANISM:	No.	Amount	No.	Amount	Amount
Research centers:					
Basic research.......	15	$19,918,000	15	$19,940,000	+$22,000
Clinical/comprehensive	41	82,970,000	41	83,064,000	+94,000
Subtotal, centers....	56	102,888,000	56	103,004,000	+116,000
Other research:					
Research career program	123	8,323,000	123	8,323,000	
Cancer education.......	29	2,942,000	29	2,942,000	
Total, research grants.	208	11,265,000	208	11,265,000	
Training :	FTTPs		FTTPs		
Individual awards....	178	4,577,000	178	4,577,000	
Institutional awards.	1,225	31,216,000	1,225	31,216,000	
Total, training........	1,403	35,793,000	1,403	35,793,000	
Research & development contracts...........					
Research management and support.........		4,375,000		4,571,000	+196,000
Construction..........		5,006,000		1,479,000	-3,527,000
Total, NCI............		159,327,000		156,112,000	-3,215,000

National Cancer Institute

Resource Development

CANCER CENTERS SUPPORT

Purpose and Method of Operation

The Cancer Centers Program supports multi-disciplinary cancer research efforts in a variety of institutions across the country. These centers are responsible for implementing a major portion of the National Cancer Program. As a group, cancer centers are engaged in all aspects of cancer research, including basic, clinical, and cancer control. They provide a standard of excellence in detection, diagnosis, treatment, rehabilitation, prevention and control, and continuing care and serve as a resource in their regions.

The types of centers include laboratory centers engaged in basic research, clinical centers emphasizing patient treatment research, and comprehensive centers which engage in all aspects of cancer research, including cancer prevention and control. A fourth type of center, the Consortium Cancer Center, stimulates and facilitates multi-institutional collaboration and interacts with regional public health agencies and other organizations that have the ability to conduct programs of cancer prevention and control.

Cancer center grants provide support for partial salaries of selected staff, for the operation of shared resources and services of the center, and for administration of the center. The grants also provide developmental funds for recruitment of new faculty and establishment of new shared facilities. The grant support they receive stimulates and promotes interdisciplinary collaboration, coordination, and research efficiency through centralized multi-user facilities and shared equipment.

The Centers are dynamic institutions possessing the capacity for organizing new programs of research which can take advantage of current and important findings that address critical and timely research questions. They are suited not only to engage in the most advanced cancer science of the day, but many are oriented toward the transfer of laboratory findings to the bedside and to the neighboring community populations. Laboratory scientists, clinicians, epidemiologists, and educators are able to work together and to benefit from each other's expertise in effective, interdisciplinary programs. More emphasis is now being given to their responsiveness on a national scale to participate in timely clinical trials and in increasing the total number of cancer patients nationwide that can be placed onto clinical trials.

In April 1989 the Institute of Medicine (IOM) released its Report on a Stronger Cancer Centers Program, commissioned by the Congress. The report was very supportive of the Cancer Centers Program and recommended several enhancements to the center core grant mechanism. During the next five years the NCI will depend heavily on cancer centers to fulfill many of its objectives. The NCI is currently in the process of developing a strategic plan to serve as a guide for the future, expanded role of cancer centers in helping the NCI establish and implement high priority activities of the National Cancer Program.

Rationale for the Budget Request

The 1991 estimate of $104,588,000 represents an increase of $159,000 from the 1990 estimate. This request for an increase in the FY 1991 budget will avoid a further decline in the number of centers throughout the Nation which receive NCI core grant support, and will permit a level of funding necessary to ensure that the critical role of cancer centers in the National Cancer Program is maintained and fully realized in the future.

Cancer centers are an effective way for the NCI to accelerate the pace of cancer research. The institutions that receive core grant support must commit to Cancer Center Directors the space, personnel authority and budget authority to promote interdisciplinary research that takes advantage of and facilitates new research opportunities. This center concept employed by the NCI during past years has stabilized the existence of organizational decision networks that horizontally crosscut the departmental structures of the best educational and non-profit research institutions in the country. With these institutional organizations in place, the NCI can begin to link centers with each other and with the NCI into a national matrix that will utilize resources and take advantage of research opportunities even more effectively, placing further emphasis on the involvement of centers in the NCI priority-setting processes and the movement of research findings to the bedside.

Core grants provide the Center Directors and all scientists affiliated with the cancer center developmental funds to test new research ideas and explore new opportunities for enhancing the research and outreach programs of the center. Many young scientists, research physicians, and epidemiologists began successful careers because of the availability of developmental funds and because of the flexibility provided to centers to make decisions and have sufficient resources available at the local level. Many of the initial new efforts of centers to evaluate and develop plans for cancer control, prevention and intervention studies are the result of core grants.

Cancer centers represent the best opportunities for NCI to move basic discoveries into the clinical setting. Cancer centers can accrue patients for clinical trials and other kinds of studies far more successfully than local hospitals and institutions that lack recognition from the National Cancer Institute. This not only provides the NCI with a resource for rapidly testing new therapies such as the interleukin-LAK trials, but also the opportunity to work with centers in pursuing how best to increase accrual of cancer patients into clinical trials and allow for the more widespread and thorough testing of increasing opportunities for improving cancer diagnosis and cancer treatment. The recent major breakthrough in the treatment of colon cancer with 5-fluorouracil and levamisole was made possible in part by the statistical shared resources available through a core grant. Finding new ways to link cancer centers with each other and with the NCI will further improve the priority setting process and the effectiveness of clinical trial programs supported by the NCI.

Cancer centers provide the most cost-effective way to introduce and maintain sophisticated technology, data resources and research resources for the scientific community. The widespread use of monoclonal antibodies, flow cytometry, molecular genetic technology, tissue culture, biostatistics and epidemiology data bases, tumor registries, oligonucleotide syntheses, transgenic mice, peptide synthesis and animal resources in cancer research is in part due to the availability of funds for shared resources on NCI core grants. The investment of cost and time for individual groups of investigators to gain rapid access to the above technologies and resources would be many-fold greater and possibly unrealistic to approach in any other manner. There is no doubt that shared resources and services supported by core grants provide stability as well as increased opportunities in cancer research. The many statistical data resources available in cancer centers throughout the country today now serve as key resources for a high proportion of the large clinical trials supported by the NCI.

Cancer centers represent an important factor in providing stability to the cancer research community. By providing partial salary support to key investigators in cancer centers, the NCI demonstrates a commitment to these individuals. Because of this strong NCI commitment, institutions provide further support to these same researchers when the availability of Federal funds to support research becomes unstable and unpredictable. Cancer centers preserve and stabilize the human resources needed for the research of the future.

Many cancer centers are already approaching the special problems of cancer in minorities and the elderly through the flexible use of core grant funds. The implementation of the new NCI guidelines for acquiring comprehensive cancer center status will increase substantially the outreach, prevention and education activities to special populations with disproportionate cancer incidence and mortality, as well as improve information transfer to the general populations in local and regional communities.

Cancer centers are awarded support because of the overall competitive excellence of their basic to clinical to control research base. This reputation for excellence has and continues to be an effective tool for cancer centers to use in obtaining State, local and individual funds to further support and develop the diversity and utility of their research, prevention and education activities.

Cancer centers currently represent a cost effective, flexible, scientifically and organizationally sound way to promote progress in cancer prevention, diagnosis, treatment and control. In addition, future strategies for moving basic discoveries to the bedside will heavily rely on working with and using cancer centers to facilitate the implementation of priorities of the National Cancer Program.

RESEARCH MANPOWER DEVELOPMENT

Purpose and Method of Operation

The NCI research manpower development programs are aimed at recruiting and training research scientists and educators who will provide the infrastructure for cancer research during the next several decades. An important aspect of the program is to provide a stable population of scientists who are capable of pursuing independent research in the areas of cancer cause, prevention and control, detection and diagnosis, treatment and rehabilitation. Another area of concern and emphasis is the recruitment and training of physician investigators in order to bring the clinical perspective into the research arena. Specific cancer education programs have been developed to stimulate and improve knowledge about cancer in medical, dental, nursing and schools of public health. A corollary of these education and laboratory programs is to attract and recruit students into biomedical research careers, particularly those from underrepresented minority groups.

The primary mechanism for achieving these cancer training objectives is the peer-reviewed grant award. Three program areas, using a variety of grant mechanisms, are used to recruit and train a broad spectrum of trainees, including high school minority students, pre- and postdoctoral basic science students and junior and senior clinicians. Program guidelines are periodically revised and special announcements made in order to address specific training gaps to meet changing scientific and clinical manpower needs.

The National Research Service Award (NRSA) Program supports individual research trainees through Predoctoral, Postdoctoral and Senior Fellowship grants. Research training awards are also made to institutions through Institutional Training Grants. Fellows and institutional grantees are selected on a nationwide basis by means of a rigorous, competitive peer review system which thoroughly evaluates the candidates' research potential, preceptor training experience, track record, and institutional resources and commitment. This program provides basic, long-term, stable support in an excellent peer-reviewed environment which is essential for the research training of young scientists. It provides a nucleus of well-trained future scientists who on average are more successful in obtaining independent research grant support than their non-NRSA counterparts. These awards support research training projects across the broad spectrum of cancer programs including cause and prevention, detection and diagnosis and treatment.

The NCI Research Career Program consists of four distinct grant mechanisms available to scientists and physicians at different stages in their careers. These mechanisms all have in common the objective of providing three to five years of full-time support to permit individuals to develop independent research skills and experience in the basic sciences and in clinical research.

The Research Career Development Award allows young cancer scientists who have demonstrated research capability and a high academic potential to devote their full-time efforts to conduct research in an excellent, peer-reviewed training environment. The program provides a five year period of stable support to facilitate the transition of the young scientist from assisting in a laboratory under preceptor supervision to becoming a fully independent investigator. Graduates of this program have a high probability and an excellent track record of becoming research academicians.

The Preventive Oncology Academic Award is used to recruit and train professionals at the postdoctoral level from a variety of backgrounds for career development in cancer prevention and control research. These awards and trainees also serve to strengthen the preventive oncology and cancer education programs at their sponsoring institutions. In addition, the trainees are eligible for an optional assignment at the National Cancer Institute to work on cancer prevention intervention or etiology projects for three months or more.

The Clinical Investigator Award is aimed at recruiting physicians who have completed their clinical residency and have been exposed to the basic concepts of the scientific method with some research experience. This award provides them with three to five years of training in basic or clinical cancer research in order to prepare them for an academic-research career.

The Physician Scientist Award has the same general objective of preparing physicians for an academic-research career. However, it is focused on recruiting recent physician graduates who require additional coursework on the principles of basic research as well as laboratory rotations to learn methodology before pursuing an intensive laboratory research project.

The NCI Cancer Education Program supports four different types of awards: Institutional grants for training doctoral-level candidates in cancer prevention and control; support for high school, college, medical, dental, nursing and public health students to work in cancer research laboratories during their non-school time; a one time, non-renewable award to design, implement and evaluate a nutrition curriculum with a focus on cancer for undergraduate schools; and, support for short-term training courses in response to specific NCI announcements.

Rationale for the Budget Request

The 1991 budget estimate of $49,879,000 represents an increase of $146,000 from the 1990 estimate. The program plans for 1991 are as follows:

NATIONAL RESEARCH SERVICE AWARDS - A 1991 estimate of $35,793,000.

The requested budget for 1991 will provide for 1,403 FTTPs of whom approximately 509 will be predoctoral students and 894 will be postdoctoral positions. They will be funded through 178 individual fellowships and 178 institutional training grants. The 1991 level maintains FTTPs at the 1990 level.

This budget will continue the support for long-term, broad-based, cancer research training. The commitment to this traditional program is particularly important since it provides the type of peer-reviewed research training most likely to encourage and produce research academicians. The level of support and degree of stability for both training and research programs are critical factors in attracting and retaining the best students in scientific training programs in competition with many other attractive careers.

NCI will proceed with intensified efforts to recruit and train significant numbers of underrepresented minorities through the Institutional Training grant program. All applications to this program will contain Minority Recruitment Plans detailing how grantees plan to achieve an increase in the number of minority scientists supported under their training grants. NCI program staff will also provide educational information and other assistance to aid training grant directors in achieving these goals. The FY 1991 budget will continue the support for the Surgical Oncology Training Program which was begun in FY 1988. Additional efforts will continue to be directed at resolving shortage training areas in preventive oncology, cancer prevention and control sciences, epidemiology, biostatistics, nutrition, oncology nursing and physician-investigators.

RESEARCH CAREER PROGRAM - A 1991 estimate of $8,323,000.

Highly promising Research Career Development candidates, as well as Clinical Investigators and Physician Scientists will be provided stable support at the current level. Guidelines for the latter two programs will be revised and strengthened. A Graduate Research Committee or similar oversight body will be established to plan, follow and evaluate the research career training of physician candidates. The objective will be to increase the efficiency of these programs in producing well-trained physician-scientists.

Recent studies continue to emphasize the potential for major reductions in cancer incidence and mortality which would result from the application of prevention strategies. However, the cadre of cancer prevention scientists is still too small to fully exploit research leads. Efforts will be made to increase the number of Preventive Oncology Academic Awards.

CANCER EDUCATION PROGRAM - A 1991 estimate of $2,942,000.

The FY 1991 level will continue support for new cancer-nutrition and chronic disease prevention awards which were initiated in FY 1988.

There is no single academic department or discipline which has the full capability for training candidates for a research career in cancer prevention and control comparable to training in the traditional biomedical disciplines. Efforts will be made to establish excellent research training programs involving the principles of disease prevention, behavioral sciences and population intervention strategies and experimental design. Collaboration between departments and institutions will be encouraged to provide the complex, multidisciplinary type of curriculum essential for training in this area.

Most U.S. scientists are white males who will comprise only 15 percent of the work force entrants by the year 2000. It is estimated that one in three U.S. students will be a minority by that year. NCI staff plans to utilize the program supporting student research laboratory experiences to recruit more underrepresented minorities. Since it is necessary to expand the pool of available minority science graduates, high school students will be a prime target. Preceptor role-models will act as career counselors and encourage students to pursue math and science courses and to enroll in college as science majors.

CONSTRUCTION

Purpose and Method of Operation

The NCI Construction Program provides funds through the award of peer-reviewed grants and contracts to cancer research institutions across the nation for construction, renovation, replacement or maintenance of the infrastructure for cancer research. In addition, support for the renovation and upgrading of facilities, on both the Bethesda campus and at the Frederick Cancer Research Facility, is funded through this authority.

Support is provided for facility development and expansion of basic research laboratories, a small number of clinical research facilities, and animal and core facilities for existing, developing, or expanding peer-reviewed cancer research. This program is a resource that serves all extramural research activities by augmenting institutional facilities that are essential for the conduct of cancer research.

Because new research initiatives often times cannot be undertaken in the absence of adequate and safe facilities, the development of new technologies and the provision of appropriate physical environments to support these innovations continues to be a program goal. The NCI construction program has historically been a crucial element in assuring a strong infrastructure for basic and clinical research throughout the country.

Rationale for the Budget Request

The 1991 budget of $1,479,000, a decrease of $3,527,000 from the 1990 estimate. The program plans for 1991 are as follows:

Funds are requested for the repair and improvement of existing facilities at the Frederick Cancer Research Facility. Major mechanical systems such as heating, ventilation and air conditioning have been in continuous operation for 20 to 30 years and are in need of an upgrade to prolong their useful lives. In addition, demands for high level containment facilities for AIDS and other virological research require that these facilities be upgraded to meet necessary standards of operation so that ongoing research efforts can continue to be provided.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Cancer Prevention and Control

Authorization: Indefinite

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
PROGRAM ACTIVITY:						
Prevention & control	178	$79,798,000	187	$80,542,000	+9	+$744,000

MECHANISM:	No.	Amount	No.	Amount	Amount
Research management and support..........		$5,311,000		$5,556,000	+$245,000
Cancer prevention and control:					
Inhouse.................		13,318,000		14,254,000	+936,000
Grants..................	95	22,475,000	95	22,523,000	+48,000
Contracts..............	113	38,694,000	113	38,209,000	-485,000
Total, NCI.............	208	79,798,000	208	80,542,000	+744,000

National Cancer Institute

CANCER PREVENTION AND CONTROL

Purpose and Method of Operation

The Cancer Prevention and Control program of the National Cancer Institute consists of four component programs which bridge the gap between basic and clinical research and health practices. Research proceeds in a step wise fashion, from clinical trials which validate the efficacy of new regimens, to defined population and demonstration studies that evaluate technological effectiveness in practice.

The Cancer Prevention Research Program develops and evaluates methods, technologies, and intervention strategies for the prevention of cancer. It includes the full range of research from laboratory and clinic-based studies to large-scale population-based validation studies.

The Cancer Control Science Program administers intervention research using strategies that have the proven potential to reduce cancer incidence, morbidity, and mortality rates. The Program also monitors basic, clinical, behavioral, and health promotion research activities to identify new intervention strategies with the potential for national application. The Program focuses particular attention on the development of intervention research that will reduce the disproportionate burden of cancer among minority and underserved populations.

The Community Oncology Program is designed to improve the delivery and application of state-of-the-art cancer treatment, continuing care, rehabilitation, and cancer screening and early detection. Research on the Cancer Care Delivery System also is supported in order to improve diffusion and remove the barriers to the application of state-of-the-art care. In so doing, the program both expedites research and enhances the diffusion of new clinical results into practice.

The Surveillance Program, while not funded through the Cancer Prevention and Control mechanism, is the core component of the NCI cancer surveillance system and tracks the impact of cancer research and cancer control efforts on cancer morbidity and mortality. A complete description of the Surveillance Program may be found in the Detection and Diagnosis section of this document.

Rationale for the Budget Request

The 1991 estimate of $80,542,000 represents an increase of $744,000 from the 1990 estimate. The program plans for 1991 are as follows:

CANCER PREVENTION RESEARCH - A 1991 estimate of $28,687,000.

Nutrition and Cancer Studies

Because as much as 25 to 35 percent of cancer mortality could be related to diet, nutrition studies seek to establish an association between dietary intake of fiber, micro- and macronutrients, vitamins, minerals or other food stuffs and the prevention or development of cancer. NCI believes that changes in dietary patterns could have a significant beneficial effect on cancer incidence and mortality.

Much of our knowledge about the relationship between micronutrients and cancer comes from studies in which serum or red blood cell nutrient levels have been correlated with cancer incidence. Although blood micronutrient levels are presumed to reflect tissue levels, human data in this area are limited. The appropriateness of using blood levels to reflect tissue nutrient composition is a critical issue since it is likely that at least in part, micronutrients exert their influence on cancer through actions occurring in specific tissues. Studies are planned to obtain data on tissue micronutrient content and its relationship to blood levels.

A new program will focus for the first time on the potential human benefit of dietary supplementation with edible fruits and vegetables. Recent reports indicate that some new food products, e.g., garlic supplements, soluble carotenoid products and flax seed products, may modulate cancer risk in humans. Studies are being planned to determine the effect of commonly consumed phytochemicals on the known metabolic pathways that detoxify drugs and to expand and apply research leads to high-risk populations. Knowledge of phytochemical constituents of fruits and vegetables, potential rich sources of cancer preventive natural products, is essential for the selection of plant foods to be tested in dietary modification studies and for providing a scientific rationale for dietary recommendations on cancer prevention.

An ancillary study to the ongoing US-Finland Studies of Nutrition and Cancer described under "Intervention Studies" below, is being initiated to determine the effect of beta carotene and/or alpha tocopherol supplementation on the development and progression of chronic atrophic gastritis, a condition involving malignant changes in the gastric mucosa. These premalignant changes in the gastric mucosa and their degree of severity can be measured by plasma markers, pepsinogen I and II, as well as by endoscopy. Dietary intervention studies are planned for population groups at high risk for gastric cancer using chronic atrophic gastritis as an indication for gastric cancer risk. The study will test whether a dietary intervention program will result in temporal stabilization or a reduction in the degree of severity of gastric lesions, thereby preventing or delaying the onset of gastric cancer.

Laboratory for Nutritional and Molecular Regulation

The intramural Laboratory for Nutritional and Molecular Regulation is continuing investigations on the possible interactions between energy intake (calories) early in life and cancer. The initial work in animals will lead to clinical metabolic studies concerning the relationships of a number of nutrients/calories to neoplastic change in man. Work is soon to begin on methods for analysis of vitamin A and related compounds. These results will be important to future clinical studies involving these compounds. Early in FY 1990, the nutrition research group occupied its balance of space assigned at the Frederick Cancer Research Facility. This group will continue to conduct research on the relationship between energy intake, and cancer.

Studies will begin on the methodology of vitamin A and related compounds to obtain information essential to designing clinical trials of these compounds in humans. Other research will be initiated on the relationship of cellular and molecular mechanisms of tumorigenesis as related to nutrients.

Chemoprevention

The goal of chemoprevention is the inhibition of carcinogenesis. A growing body of epidemiologic, basic science and clinical trial data support the efficacy and merit of chemoprevention research. Until recently, the elimination of carcinogenic agents and early detection of precancerous lesions dominated the field of cancer prevention research. Now, the understanding of biochemical mechanisms of carcinogenesis has progressed to the point where other strategies for intervention in the carcinogenic process also can be carried out. Knowledge about initiation and promotion of carcinogenesis, evidence of the factors which modify the course of neoplastic cell growth, and contributions of molecular biology in defining the critical events of neoplastic transformation provide the rationale and direction for chemoprevention research. Laboratory and clinical studies of cancer prevention agents now have 19 agents undergoing clinical testing, 250 agents in preclinical investigations and 800 agents under review.

A number of human efficacy intervention trials are currently being sponsored. Endpoints in these studies include overall incidence of cancer, incidence of specific cancers, the rate of regression, and/or progression of preneoplastic changes, and changes in cellular or biochemical parameters associated with tumor regression or progression. Study participants include volunteers from the general population; populations at high risk for cancer because of occupation, life style, or place of residence; persons with preneoplastic lesions, and/or persons with previously treated cancer.

Twelve of these studies are so-called "intermediate endpoint" studies. Intermediate endpoints are biological and biochemical parameters which may serve as surrogate markers for cancer endpoints in chemoprevention trials to help us learn more about the underlying mechanisms of the neoplastic process. Additionally, they may be employed in cancer risk reduction trials to enhance our understanding of factors related to ultimate chemopreventive effects and help us learn more about the underlying mechanisms of the neoplastic process. Four of the ongoing trials focus upon those at high risk for the development of colon cancer. All involve those with a previous colon adenoma, a lesion generally agreed to be a precursor for colon carcinoma.

Intervention Studies

A broad array of efficacy studies using animal models has been implemented to address breast, lung, colon, bladder, and skin cancers. These investigations employ agents related to the retinoids, beta-carotene, vitamin E, selenium, and other substances. A recent clinical prevention trial demonstrated that high fiber was associated with polyp regression; this suggests that a dietary fiber-grain intake of at least 11 grams per day may inhibit polyp development, which in turn, may reduce the risk of colon carcinoma.

Many other trials are underway including: a major intervention study based in Finland to assess the role of fats, selenium, and vitamins A, E, and C in breast cancer development, and to evaluate the relationship of the intake of various nutrients to subsequent cancer, particularly of the breast, colon, and lung; a 34,000-subject trial in China to prevent esophageal cancer using multiple vitamins and minerals in order to develop an understanding of the genetic as well as environmental influences that are involved in the etiology of human esophageal cancer; a study involving approximately 22,000 U.S. physicians to determine whether a routine administration of beta carotene will prevent lung cancer; and skin cancer studies to determine the effectiveness of a number of different supplements such as retinol and 13-cis-retinoic acid, beta carotene, and beta carotene in combination with ascorbic acid and alpha-tocopherol.

Large bowel adenomatous polyps present a unique opportunity to conduct an intervention trial because of their high prevalence rate in the general population, the high polyp recurrence rate in those who have undergone polypectomy, and the link between polyps and cancer. It is generally accepted that large bowel adenomas are a requisite precursor lesion for most large bowel cancers. Given the strong evidence for the polyp-cancer sequence, an intervention that reduces the recurrence of large bowel polyps would have a strong likelihood of reducing the incidence of large bowel cancer. The major objective of a new study is to determine whether an experimental large bowel cancer "risk reduction" diet that is low fat, high in fiber, and vegetable- and fruit-enriched will decrease the recurrence rate of large bowel adenomatous polyps. This will be a multi-center randomized controlled trial involving 2,000 men and women. Study participants will be randomized into either the experimental diet group or a control group with a usual diet. Recruitment will take up to two years, and the follow-up time from randomization is four years. The study will also investigate the relationship between the dietary intervention and several putative intermediate endpoints in large bowel carcinogenesis to evaluate the correspondence between them and subsequent neoplastic adenoma formation.

A broad variety of other studies are needed to enable scientists to more fully explore the kinetics and potential toxicities of agents that will be used in intervention studies and to understand the potential mechanisms of action of diet changes on cancer prevention. Studies being planned include clinical nutrition studies that will evaluate the kinetics of various forms of ingested vitamin C, both in foods and supplements, the response of hormones to weight loss in overweight women, and the influence of ingestion of putative carcinogens from cooked meats on fecal mutagens. Plans are also being developed to follow a large cohort of retired persons to allow better evaluation of the relationship of diet, particularly factors with relatively low variability in our U.S. diet, to cancer in the elderly.

CANCER CONTROL SCIENCE - A 1991 estimate of $18,981,000.

Cancer in Minority Populations

NCI has established a major initiative to address the cancer needs of U.S. minorities. Based on comparative data of cancer incidence, mortality and survival, the initial focus has been on intervention studies in Black Americans, with the goal of reducing or eliminating the differentials in cancer incidence, mortality and survival between blacks and whites by the year 2000. More recently, programs have been initiated which address the disproportionate cancer burden experienced by Native American populations, including American Indians, Alaskan Natives, and Hawaiian Natives as well as Hispanic populations.

National Black Leadership Initiative

The application of existing knowledge to improve the health status of Black Americans is being accomplished in part by the Black Leadership Initiative undertaken by the National Cancer Advisory Board. Through a series of public meetings held in six major U.S. cities with large black populations, leaders from the business community have been drawn into a partnership with the NCI to address cancer prevention and early detection opportunities for Black Americans. This effort has enhanced the level of understanding among these community opinion leaders who are now directing their energies toward curbing some behaviors especially detrimental to the health of Black Americans. Most notably, health promotion messages have been developed with respect to cigarette smoking, dietary practices and the utilization of effective early detection procedures.

Intervention Research in Other Minorities and the Underserved

A program of intervention research to address cancer problems in Hispanic populations has begun, directed at communication, language and health service barriers to cancer control. Multiple data sets have been used to evaluate the risks and rates of cancer among the various Hispanic subpopulations in order to provide an epidemiologic framework for this intervention research approach. Special attention will continue to be given to preserving positive health behaviors associated with the Hispanic culture while simultaneously developing interventions to address the obstacles to effective cancer control that are experienced by this population.

Modeled after the intervention studies in the black and Hispanic populations, similar research projects have been developed to address the cancer control problems found among the Native American populations: American Indians, Alaskan Natives, and Hawaiian Natives. Although small in numbers, these populations experience excessive cancer rates that appear to be related to their heavy concentration in the lowest socioeconomic categories. Cultural, spiritual, historical and language barriers also play a role in their delay in seeking prompt diagnosis and treatment. For this reason, cancer control networks are being established among both Hawaiian Native and American Indian populations modeled after the existing cancer control network for the Black population. Existing data sets are being used and new data sets are being developed to assist researchers in determining where they may best concentrate their efforts among these communities.

Additionally, intervention research programs are being developed to address the severe and excessive cancer burden prevalent among older persons, low income persons, inner city residents and other medically underserved groups. Future efforts will be directed at identifying deficiencies in the medical/health care system that deter minorities from fully utilizing available resources. Examples of planned activities include:

- A Cancer Prevention and Clinical Research in Underserved Populations program to integrate and deliver a full spectrum of cancer prevention, screening and early detection, and treatment services to high-risk minority and low-income groups will be developed.

- An Aging Population Cancer Control and Prevention Initiative to study high-risk aging special populations will be developed, in concert with the National Institute on Aging, and implemented.

- Culturally relevant prevention education tools for Native Americans, including videos and brochures will be developed and disseminated.

- A Patterns of Care and Socioeconomic Status for Black Patients Study will analyze access issues and impact on low-income patients.

Breast Cancer Screening

Breast cancer screening is a proven life-saving technology that is vastly under used. NCI has launched a network of coordinated studies to evaluate health promotion strategies to improve the utilization of effective technologies for breast cancer detection. The studies are underway in various communities in seven states: California, Massachusetts, New Jersey, New York, Pennsylvania, North Carolina and Washington. Baseline studies were initially conducted to determine the current level of practice in mammography and clinical examination of the breast. The baseline surveys indicate that barriers for mammography differ for women as compared to physicians, and that utilization is well below the recommended frequency. The studies have developed strategies to increase the use of mammography by both health care providers and their patients. NCI, in collaboration with the National Institute on Aging and the Health Care Financing Administration, is planning to supplement grants that evaluate and promote the new Medicare coverage of mammography for women over age 65.

Worksite-Based Interventions

The worksite is important for the dissemination of health-related information and is potentially a very strong force for behavior change. Because individuals spend so much time at work, it presents a unique opportunity for health promotion intervention. Current emphasis on health and well being provide opportunities to develop interventions that will address the modification of behaviors associated with cancer risk as well as the support of positive health promoting behaviors. NCI has recently initiated and funded an effort to evaluate worksite health promotion activities. This initiative will design, implement and evaluate nutrition, screening, and tobacco control efforts that will complement existing disease and occupational health programs. The nutrition component will include modifications in the offerings of cafeterias and vending machines, as well as educational development. The screening component will provide screening, follow-up, and education on screening and state-of-the-art treatment options. The tobacco control interventions will offer a menu of smoking cessation options and assess the effects of smoking bans on employees. The long-range strategy for this effort is to develop interventions shown to be effective in worksites which can then be disseminated on a nationwide basis.

Collaborations with Public Health Agencies

State and local health departments form a national infrastructure through which cancer prevention and control efforts may be addressed. They have statutory responsibility for public health, provide direct personal health service to a significant part of the population, have a particular orientation to the health needs of otherwise underserved populations, and are experienced in working with a broad range of community groups and agencies.

Beginning in 1987, the NCI program with state health departments has funded 22 states and one local health department to more effectively use existing data resources to develop a state cancer plan and to initiate interventions. An important part of this process is the education of state legislators about the extent of the cancer problem, what can be done about it, and the resources necessary for this response. A new grant program to develop and test interventions to increase the use of screening mammography and cervical smears in women of low income, low education, and minority groups will begin its start-up phase in the last quarter of FY 1990. By 1991, there will be (or have been) major grant-supported activity in at least 30 states.

Cancer Prevention Fellowship Program

The NCI Cancer Prevention Fellowship Program's purpose is to train and educate new cancer prevention and control scientists for a career in cancer control science and research. Since 1985 the program has trained over 20 scientists, and assisted in their placement in cancer centers, academic institutions, or health departments throughout the United States. Plans are going forward to secure residency training credit for physicians toward accreditation in preventive medicine and the MPH degree for Fellows enrolled in the program.

Cancer Control Research Program

Three complementary approaches funded through research project grants have been used to overcome the shortage of cancer control research in this country: the Cancer Control Science Program (CCSP) grants, the Cancer Control Research Unit (CCRU) grants, and the Cancer Prevention Research Unit (CPRU) grants. These grants have aided and facilitated the growth of a nationwide cohort of institutions and scientists with a high level of research expertise in the field of cancer prevention and control intervention research.

The most recent initiative, the Cancer Prevention Research Unit (CPRU) Program, is the successor to the Cancer Control Research Unit effort. These CPRUs conduct primary and secondary prevention, health promotion and preventive services research aimed at developing new intervention approaches in all areas of cancer prevention, or applying proven or state-of-the-science in interventions in the smoking and screening areas identified in NCI's cancer control objectives for the year 2000. The high level of interest in the CPRU Program has been demonstrated by the volume of letters of intent received from currently-funded and newly-interested investigators and institutions.

The CPRU portfolio includes the Los Angeles County (at UCLA in Los Angeles, California) which contains six projects which target improved breast and cervical cancer detection in primarily Hispanic East Los Angeles, through the Los Angeles County Department of Health Services. In addition, the University of Rhode Island contains four projects aimed at "accelerating the process of change for cancer prevention" through smoking control and mammography screening projects. The Seattle CPRU contains 12 projects, including a major multicenter efficacy trial of beta carotene and retinol in populations at high risk for cancer, while the one at Yale currently contains seven broad-ranging cancer control projects.

Smoking, Tobacco, and Cancer

The Smoking, Tobacco, and Cancer initiative is aimed at reducing the prevalence of cigarette smoking and the consumption of other tobacco products. Since the relationship between tobacco consumption and cancer is well-established, recent activities have focused on research designed to develop feasible, efficacious and effective programs for the prevention and cessation of tobacco use.

This initiative is pursuing a two-pronged strategy in its intervention research efforts. The first involves the study of methods that have the potential to modify behavior. The most promising intervention approaches have been targeted for evaluation in randomized trials and include school-based interventions, self-help strategies, physician/dentist-delivered interventions, mass media approaches, and community-based interventions. The other approach entails focusing research efforts on specific target populations that are at greatest risk for developing cancer or where the greatest prevention and control gains could be expected. Populations given priority for targeted intervention research in tobacco use prevention and cessation include youth, minority/ethnic groups, women, smokeless tobacco users, and heavy smokers. Between 1984 and 1987, over 50 major clinical trials of tobacco use prevention and cessation intervention strategies were begun. These trials are now producing results to guide national tobacco use control efforts.

Special Population Interventions

Intervention trials targeted to women, Black Americans, Hispanics, and smokeless tobacco users have been initiated recently. The five trials directed at women are evaluating smoking cessation programs for low income pregnant smokers, efforts to minimize post-cessation weight gain, incorporation of smoking cessation into nurses' training programs, and development of more effective self-help strategies for women. A national network of women's organizations and leaders has been established to disseminate the results of these ongoing trials as they become available in future years.

Twelve intervention trials and demonstration studies were initiated in 1985 and 1986 to address the special needs of black and Hispanic populations. These studies are evaluating population-specific information campaigns, modifications of prevention and cessation interventions, and culturally sensitive dissemination programs. As materials are developed, they are prepared for national distribution through the Office of Cancer Communications. For example, 500,000 copies of the Hispanic self-help guide, "Guia para Dejar De Fumar," have been printed and distributed nationwide.

Based upon the rapid emergence of the smokeless tobacco problem in the mid-1980s, the smoking and tobacco use research initiative in this area was expanded. Prevention and early cessation efforts among adolescent users is being emphasized in seven intervention trials. These trials are testing prevention strategies in schools, 4-H clubs, and other community settings. Additionally, a dental office-based cessation protocol is being tested among young adult smokeless tobacco users.

COMMIT - Community-Based Intervention Trial for Heavy Smokers

The Community Intervention Trial for Smoking Cessation (COMMIT) was initiated in 1986 as a randomized community-based trial involving 11 pairs of communities and more than two million people in the United States and Canada. The trial is testing a protocol of smoking cessation strategies delivered through community organizations and social institutions. A large proportion of these strategies were developed through the Smoking, Tobacco and Cancer intervention trial program.

Because individuals who smoke 25 or more cigarettes per day are at greatest risk for cancer but have shown the least reductions in smoking in the last two decades, this population is the major target of this trial. Community mobilization has been completed in all 11 intervention sites and local boards and task forces are now directing the implementation of the common protocol strategies in local media, worksites, schools, health care providers, and community agencies. Implementation and outcome results from this intervention protocol will provide a model to communities around the nation who want to establish effective community-wide smoking control programs.

ASSIST - American Stop Smoking Intervention Study

The major objective of the American Stop Smoking Intervention Study for Cancer Prevention (ASSIST) will be the achievement of the Year 2000 Health Objectives for the Nation for tobacco consumption. The ASSIST initiative, the largest and most comprehensive of its type ever conducted, will establish large-scale demonstration efforts to disseminate the smoking and tobacco use trial results in up to 20 states or large metropolitan areas and will reach up to 100,000,000 Americans. This initiative will involve a 18- to 24-month planning period and a five-year intervention period when the actual programs are implemented.

This initiative is being jointly conducted by NCI and the American Cancer Society (ACS). The ACS and local health departments, states, or metropolitan areas will provide the leadership to form coalitions of public, civic, business, labor and voluntary organizations to implement ASSIST. These coalitions will form the basis for permanent smoking and tobacco prevention interventions after ASSIST funding has ended. As part of the ASSIST preparations, NCI has prepared a "Guide to Public Health Practice: State Health Agency Tobacco Prevention and Control Plans" in conjunction with the Association of State and Territorial Health Officials. Additionally, the "Standards for Comprehensive Smoking Prevention and Control" has been prepared and will serve as the technical guidelines for ASSIST sites to plan effective program efforts.

COMMUNITY ONCOLOGY PROGRAM - A 1991 estimate of $32,874,000.

Community Clinical Oncology Program

Through the Community Clinical Oncology Program (CCOP), a network of community cancer specialists, primary care physicians, and other health care professionals have access to both clinical treatment research and cancer control research studies in the areas of early detection and screening, chemoprevention, smoking, patient management, continuing care, and rehabilitation. Funding is also provided for clinical cooperative group members and affiliates to participate in cancer prevention and control research, thus broadening the network.

The 52 community programs in the CCOP, funded through May 1990, are located in 30 states and involve 250 hospitals and 2,000 physicians. Approximately 5,000 patients per year are entered onto treatment clinical trials through the CCOP, representing about one-third of the annual accrual to NCI randomized trials. In the last year, over 6,000 patients/subjects were involved in cancer prevention and control clinical trials.

Minority-Based Community Clinical Oncology Program

In general, cancer survival rates among minority populations are less than in whites. For example, data from NCI's Surveillance, Epidemiology, and End Results (SEER) Program show that the five-year relative survival rate for all cancer sites in blacks is 38.2 percent compared to 52.0 percent for whites. In addition to poorer survival outcomes, cancer incidence and mortality rates for selected cancer sites in minority populations are higher compared to whites.

One way to develop and implement effective treatment and cancer control strategies in minority populations, and thereby reduce disparities in cancer incidence, morbidity, and survival rates between whites and minority populations, is the involvement of minority populations in the clinical trials process. Available data indicate that access to the clinical trials process is a key factor in increasing minority participation in clinical research.

Since the CCOP model is an effective mechanism for linking investigators and their institutions with the clinical trials network, a Minority-Based CCOP RFA was issued in 1989 to provide minority cancer patients/subjects with enhanced access to state-of-the-art cancer treatment and control technology. Eligible applicants for this RFA must have greater than 50 percent of new cancer patients from minority populations. Through this initiative, NCI aims to meet the needs of minority cancer patients and individuals at risk for cancer by establishing a system of oncology programs for participation in clinical research trials through the NCI network. Funding of eight programs is anticipated in 1990.

New Guidelines for Comprehensive Cancer Centers

In FY 1990, NCI approved new guidelines for the designation of NCI-supported cancer centers as comprehensive. One of the provisions for comprehensiveness requires a strong base in cancer prevention and control research, while the second requires the center to be strongly involved in cancer control community outreach. These provisions will strengthen the Nation's cancer prevention and control program by increasing the base on research on cancer prevention and control and creating a stronger link between the knowledge base and application. Centers designated as comprehensive will be able to serve their communities by translating the results of cancer prevention and control research directly into the community setting. Moreover, these outreach programs will serve as models for other communities across the country.

Community-Based Cancer Care

The perception that cancer is inevitably linked with intractable pain may decrease patients' participation in screening and early detection activities and may influence patients to seek cures via unproven therapies. The availability of effective approaches to pain control and efforts to increase the public's awareness that cancer pain can be alleviated would increase the likelihood that patients will seek out appropriate cancer care. To this end, research will be supported to foster acceptance and utilization of cancer pain control protocols by health care professionals.

The challenges faced by adults who survive cancer actually begin as they undergo the treatment process. It is necessary to understand the full impact of cancer and its therapy and to test interventions which can be incorporated into the continuing care of the adult cancer patient. Also, individuals with cancer who are living at home have a complex array of needs and problems. They also experience great variations in availability and adequacy of services. Meticulous longitudinal studies of these patients are currently being analyzed. An expert panel of researchers and practitioners will review the findings and set priorities for intervention studies.

The vast majority of cancer treatment is now delivered in the outpatient setting with patients responsible for symptom prevention, detection and management. Studies will continue to be supported which evaluate nursing interventions to promote patient self care and to identify characteristics and patterns under which self care is not accomplished and to target additional intervention strategies.

Intervention research will be supported which is aimed at alleviating those factors that contribute to poorer outcomes for elderly cancer patients. Based on the results of previous research, interventions may be targeted to patients as well as physicians and the health care system. An integral part of the evaluation of both treatment and continuing care interventions is an understanding of the impact on the patient. An invitational workshop will be conducted to analyze the current trends and issues and to explore the best approaches to fully integrate quality-of-life evaluation into NCI programs. Based on this analysis, research in priority areas will be supported.

Early Detection

The goal for early detection is to achieve a significant reduction in cancer morbidity and mortality through early detection and appropriate treatment. Studies to be undertaken concern screening techniques for cancers of the colon/rectum, lung, urinary bladder, ovary, and prostate. Other activities include education and dissemination of proven effective screening methods, and surveillance and evaluation studies to determine the factors which retard or increase the prevalence of screening in the medical community. New analytic techniques and alternative evaluation criteria will be studied and the search for new technologies for more effective early detection will continue. Community programs will be supported to test the effectiveness of various approaches in transferring the knowledge from research efforts into medical practice.

In order to evaluate the use and efficacy of early detection methods in the community, a clinical network of primary care providers will be employed. A request for grant applications will be issued which will study the extent that proven early detection methods are used and support an evaluation of the effects of these methods on patient populations. Another effort to increase the prevalence of early detection activities is through tumor boards. Tumor boards are a widely disseminated mechanism for continuing medical education in hospitals. These and other hospital-based educational activities represent an opportunity for increasing the awareness and knowledge of physicians and other health professionals about the early detection of cancer. Steps are underway to develop a request for grant applications directed toward institutions interested in initiating research into approaches and methods to increase the usefulness of hospital-based continuing education efforts in the area of early detection. In addition, studies to determine the number of cancers being detected through early detection methods are needed. This can be accomplished through a review of the medical records of cancer patients and through interviews with physicians and patients. These studies will be implemented in FY 1991.

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Detail of Permanent Positions

	1989 Actual	1990 Appropriation	1991 Estimate
ES- 4	14	14	14
ES- 3	7	7	7
Subtotal.............	21	21	21
GS-15	124	124	124
GS-14	188	188	188
GS-13	143	143	143
GS-12	179	189	193
GS-11	220	240	245
GS-10	1	1	1
GS- 9	177	197	202
GS- 8	50	50	50
GS- 7	203	223	238
GS- 6	124	124	124
GS- 5	73	83	88
GS- 4	30	30	30
GS- 3	5	5	5
GS- 2	2	2	2
Subtotal.............	1,519	1,599	1,633
Commissioned Officer 8...	1	1	1
Commissioned Officer 7...	1	1	1
Commissioned Officer 6...	81	81	81
Commissioned Officer 5...	46	46	46
Commissioned Officer 4...	12	12	12
Commissioned Officer 3...	5	5	5
Subtotal.............	146	146	146
Ungraded................	15	15	15
Total permanent positions	1,701	1,781	1,815

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

New Positions Requested

		1991	
	Grade	Number	Annual Salary
NCI Intramural Research			
Biologist	GS-12	1	37,079
Medical Technologist	GS-12	1	37,079
Biologist	GS-11	2	61,874
Computer Specialist	GS-11	2	61,874
Administrative Officer	GS- 9	1	25,570
Biological Laboratory Technician	GS- 9	2	51,140
Microbiologist	GS- 9	1	25,570
Program Analyst	GS- 9	1	25,570
Administrative Assistant	GS- 7	1	20,902
Administrative Technician	GS- 7	1	20,902
Biologist	GS- 7	2	41,804
Contracts Specialist	GS- 7	1	20,902
Epidemiologist	GS- 7	1	20,902
Grants Assistant	GS- 7	2	41,804
Medical Technician	GS- 7	3	62,706
Secretary	GS- 7	1	20,902
Technical Assistant	GS- 7	1	20,902
Clerk	GS- 5	1	16,876
Grants Technician	GS- 5	1	16,876
Secretary	GS- 5	1	16,876
		27	$648,110
NCI Cancer Prevention & Control			
Program Coordinator	GS-12	1	37,079
Public Health Advisor	GS-12	1	37,079
Public Health Advisor	GS-11	1	30,937
Editorial Assistant	GS- 7	1	20,902
Secretary	GS- 7	1	20,902
Administrative Technician	GS- 5	1	16,876
Clerk	GS- 5	1	16,876
		7	$186,793

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Advisory and Assistance Services

For FY 1991, the Advisory and Assistance Services budget will be $4,012,000 a reduction of $687,000. Funding for the Community Clinical Oncology Program (CCOP) evaluation contract decreased between FY 1989 and FY 1990 from the original level. This contract is scheduled to be closed out in FY 1991; the final year of this project is for data analyses and report writing, which is much less costly than the data collection phase. Funding for the series of support contracts for the Cancer Communications Program will increase by approximately $500,000 between FY 1989 and FY 1990. This contract assists in the design, development and implementation of information dissemination and education programs targeted to the public, patients, and health professionals. NCI plans to increase its efforts in reaching minority populations, the elderly and the rural poor. Most other activities will be held constant between FYs 1989, 1990 and 1991.

The National Cancer Institute has always tried to make the most efficient use of the resources at its disposal. Contract-supported consulting activities of NCI reflect the judgment that contracting for these services is the most efficient and cost effective method of providing for these services. Further, the services provided by contractors require expertise that is not represented on staff, nor is the service required on a continuing basis. It would not be cost effective to hire staff to provide these services because 1) the need for the services is time-limited, and in general, services are only needed sporadically, and 2) the contractor has the flexibility to contract, expand or shift staff to perform certain services that the government does not possess. In addition, program evaluation contracts require a degree of unbiased objectivity and detachment that in-house personnel cannot provide. These contracts provide for an examination of a particular cancer research program. The studies provide Institute managers with information on the accomplishment of program objectives and the relationship of those objectives to NCI's mission. Thus, these contracts provide to the Institute a tool to assist in program development and management decision-making. The principles of the peer review process employed at the National Institutes of Health have traditionally demanded that scientific projects be reviewed by outside (i.e., non-federal) personnel. In accordance with these peer review principles, the NCI funds advisory committee members for its National Cancer Advisory Board, President's Cancer Panel and Boards of Scientific Counselors. In addition, the services of *ad hoc* consultants who provide special expertise to committees and boards on an as-needed basis are purchased via procurement contracts. The use of in-house personnel to provide peer review services would violate the principles of peer review that are the foundation of the NIH scientific merit review process.

Policy guidelines exist in the form of OMB Circular A-120, *Guidelines for the Use of Advisory and Assistance Services*, and DHHS General Administration Manual 8-15, *Advisory and Assistance Services*. This guidance has been promulgated to make staff aware of the definition of Advisory and Assistance Services (AAS) and informational memoranda on the same subject are sent to staff reminding them of their responsibilities in this area. Each year a Consulting Services Plan is prepared identifying planned AAS procurements in the next fiscal year. The NIH Accounting System contains Common Account Numbers (CANs) that have been designated for use in identifying and aggregating costs for AAS. The NCI Research Contracts Branch affixes a designated Federal Procurement Data System (FPDS) code to all contracts which procure AAS. All contracts procuring AAS are subject to approval before award by designated approving officials whose responsibility it is to assure that the services are essential to the operation of the requesting unit, that the services cannot be provided by in-house personnel and that the services are obtained at the lowest reasonable cost. Concepts for each contract for consultant services must be reviewed and approved by the appropriate NCI divisional board of scientific counselors prior to issuance of a Request for Proposals (RFP). This review process by a board of outside experts ensures evaluation of the need for a contract for consultant services in the context of other NCI program activities and staff commitments.

TUESDAY, MARCH 13, 1990.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

WITNESSES

DR. CLAUDE LENFANT, DIRECTOR

DR. WILLIAM F. RAUB, ACTING DIRECTOR, NIH

DR. BARBARA PACKARD, ASSOCIATE DIRECTOR FOR SCIENTIFIC PROGRAM OPERATIONS, NHLBI

STEPHEN A. FICCA, EXECUTIVE OFFICER, NHLBI

JAMES WEHLING, FINANCIAL MANAGEMENT OFFICER, NHLBI

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, DHHS

Mr. NATCHER. At this time, we take up the budget request for the fiscal year 1991 for the National Heart, Lung, and Blood Institute.

And we have before the committee Dr. Claude Lenfant, the Director.

Doctor, you have appeared before our committee on a great many occasions, and as you heard me say last year and several years before that, you have a good story to tell, and we want you to tell it today.

Doctor, before you give us your statement, tell us who you have with you there at the table.

Dr. LENFANT. Thank you, Mr. Chairman.

Excuse me. On my far left is Mr. Ficca, the Institute's Executive Officer; Mr. Jim Wehling, our Budget Officer; on my right is Dr. Packard, the Associate Director for Scientific Programs; and, of course, you have met Dr. Raub and Mr. Williams.

Mr. NATCHER. Delighted to have all of you before the committee. And now, Doctor, we will be pleased to hear from you.

Dr. LENFANT. Thank you, Mr. Chairman.

In past years I have appeared before you and told you that our cardiovascular disease research programs have been very successful. Indeed, Chart 1 shows that mortality rates from these diseases continue to decline. For example, we can estimate that 187,000 additional coronary heart disease deaths would have occurred in 1987 had the death rate not declined between 1977 and 1987. Of course, this has happened because of our ever-increasing ability to diagnose and treat cardiovascular patients, especially those with coronary artery disease.

However, there is a trade off for this success, and we must not be lulled into a false sense of security. It is now clear from demographic shifts that the prevalence of coronary heart disease is increasing as shown on Chart 2. Indeed, between 1977 and 1987, there were nearly twice as many people per 1,000 population with coronary heart disease in 1987 then there were in 1977.

With increase in prevalence, there is an increase in cost. Looking only at the morbidity costs which include expenditures for hospital care, physicians, and other health services such as drugs and nursing home care, we see that the morbidity costs on Chart 3 have increased 150 percent between 1977 and 1987. In terms of dollars, in 1987 the medical care of coronary heart disease alone was $18.4 billion. Of course, no one would debate that this is a tremendous cost.

However, the important consideration from the viewpoint of the American people is that remarkable progress has been accomplished through research, and that this progress has considerably reduced the potential cost to the nation. Looking at only one component of the morbidity cost, i.e., the duration of the hospital stay, we know that between 1977 and 1987 it decreased from 10.4 days to 6.5 days. Hence, between 1977 and 1987, that alone represents a true savings of $34.7 billion to the American people. In 1987, Chart 4 shows that the morbidity cost of coronary heart disease alone would have been $28.2 billion instead of $18.4 billion.

As I said earlier, when we look only at the costs of hospital stays between 1977 and 1988, the saving was $34.7 billion. During this period of time, the cumulative appropriation to the Institute for all its programs in heart, lung, and blood disease was $6.9 billion.

I have prepared Chart 5 to summarize the major advances in heart and blood research that contributed to this reduction in average hospital stay and dollar savings.

Although we have reasons to be pleased with our progress, we are still confronted with a major problem. Our concern for the situation I just described is matched only by our concern with the increased death rate from chronic obstructive pulmonary diseases (or COPD) that we continue to observe year after year, which is illustrated on Chart 6.

These problems, Mr. Chairman can be solved only by intensified research to identify early on those Americans who are at risk of cardiovascular and pulmonary disease, and by developing more effective therapies. My written statement describes an array of research avenues that we are actively pursuing on heart, lung, and blood disease. It also describes some of our achievements with public health and cost saving benefits.

These accomplishments reflect the breadth of our program in basic, clinical, demonstration and education research. To conclude, I would like to emphasize the contributions of our Centers-supported clinical research. Indeed, much of the progress in coronary heart disease that led to a shorter hospital stay between 1977 and 1987, on Chart 5 has resulted from work done in our Centers of Research. I would be pleased to answer any questions the Committee may have. Thank you, Mr. Chairman.

[Charts and the prepared statement of the Director, National Heart, Lung, and Blood Institute follow:]

Coronary Heart Disease Death Rates

U.S., 1977-1987

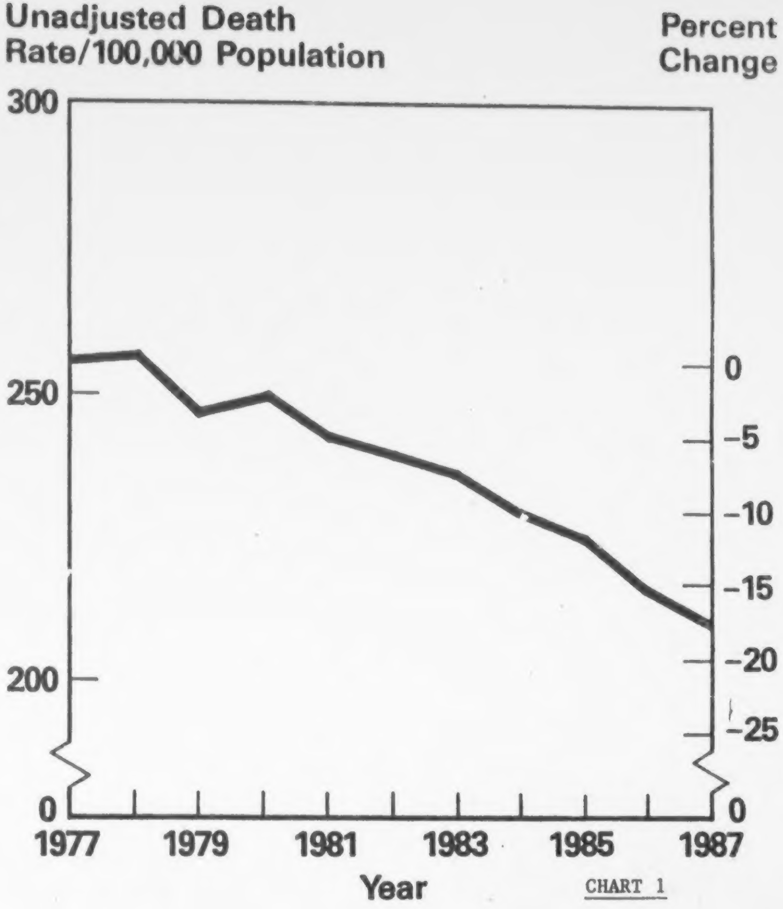


CHART 1

Coronary Heart Disease Prevalance

U.S., 1977-1987

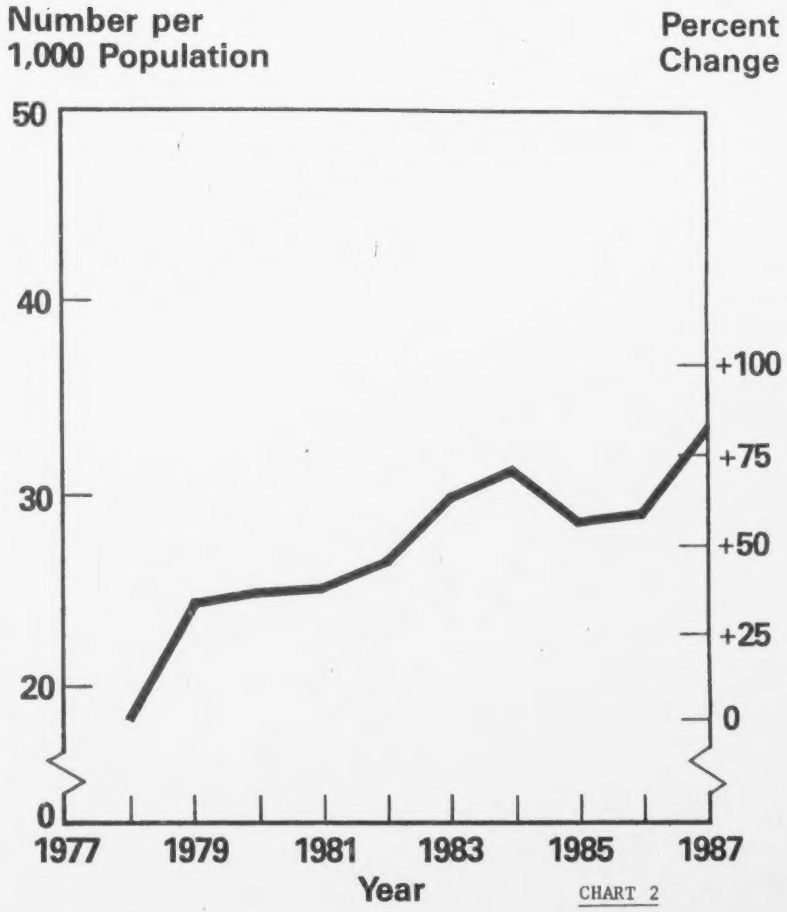


CHART 2

Coronary Heart Disease Morbidity Costs
U.S., 1977-1987

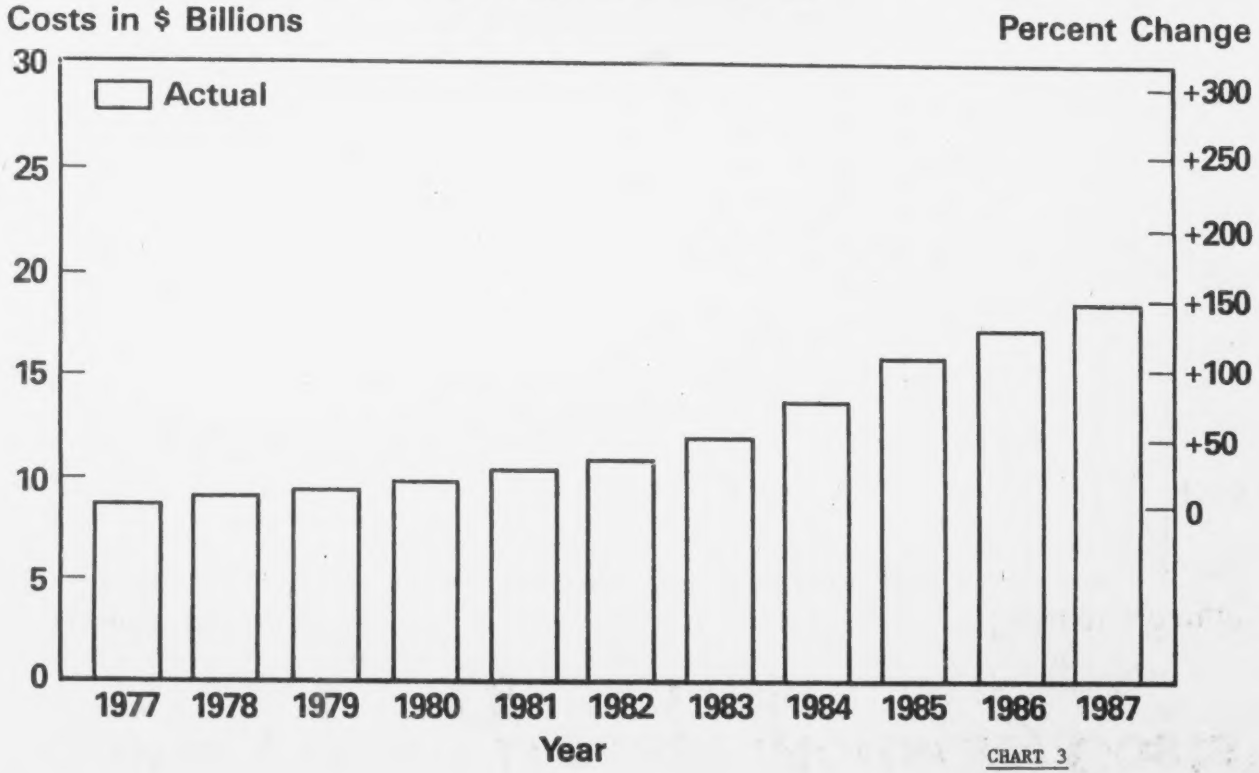


CHART 3

Coronary Heart Disease Morbidity Costs
U.S., 1977-1987

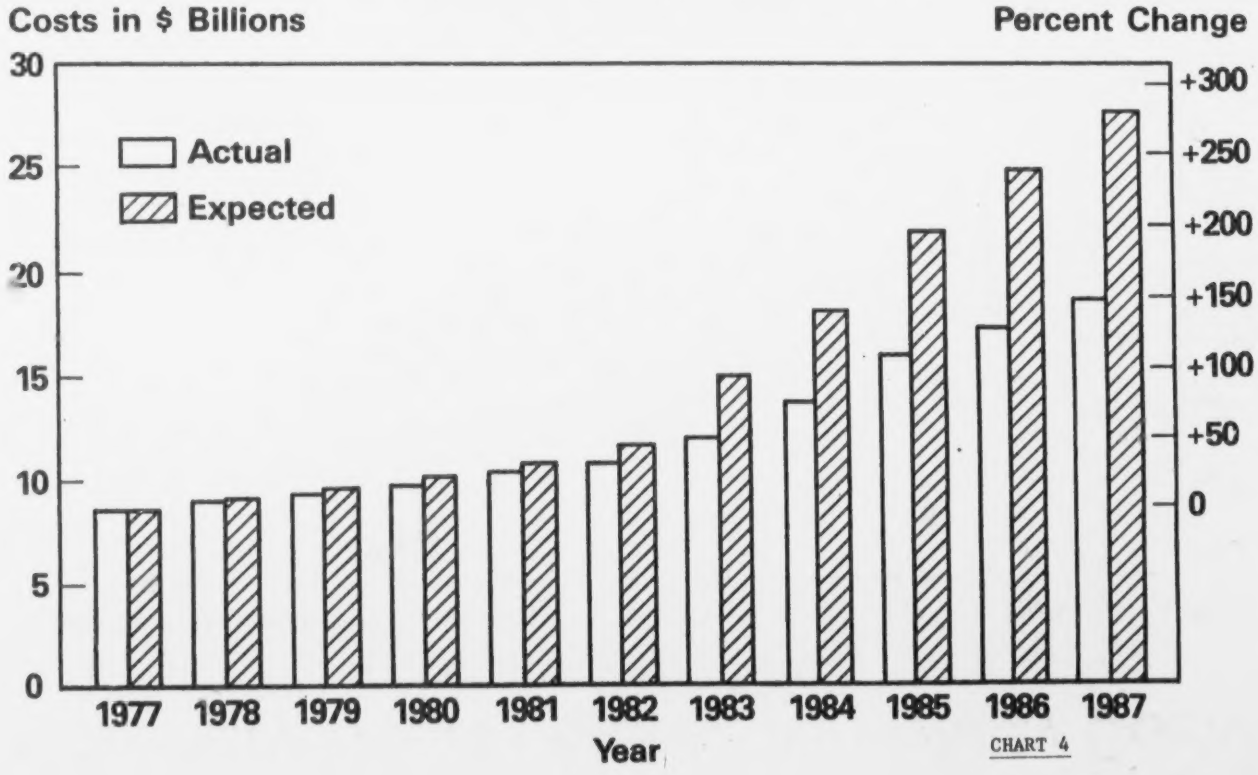


CHART 4

Length of Hospitalization for Patients with Heart Attack

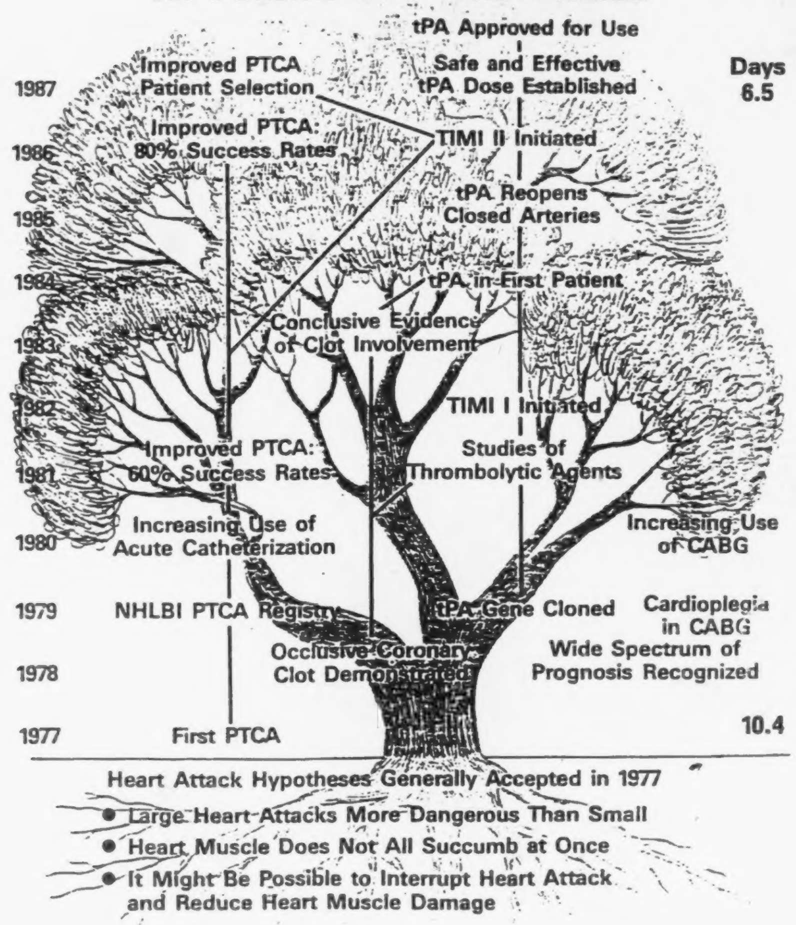


CHART 5

COPD
Death Rates
U.S., 1977-1987

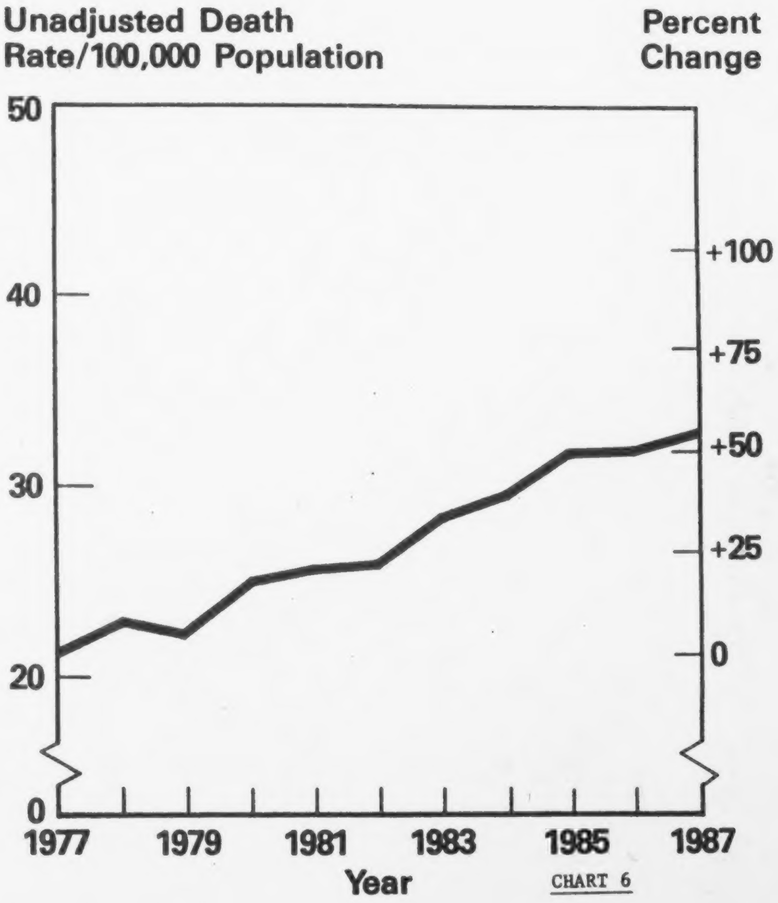


CHART 6

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Heart, Lung, and Blood Institute

It is my pleasure to speak to you once again about the programs of the National Heart, Lung, and Blood Institute (NHLBI). Since its inception, the Institute has been strongly committed to disease prevention, a goal that has been greatly furthered by basic, clinical, and population-based studies designed to identify risk factors for cardiovascular, lung, and blood diseases. Interventions to reduce the impact of the three major cardiovascular risk factors--hypertension, cigarette smoking, and high cholesterol--have paid off handsomely in terms of reduced mortality. Findings from new studies are now bringing more precision to our indicators of risk for certain subgroups of the population. For example, the Framingham Heart Study recently reported results of echocardiographic studies that revealed increased left ventricular mass to be a powerful predictor of future heart problems in Blacks and in elderly persons. The recently initiated Cardiovascular Health Study, which focuses on individuals ages 65 to 90 years, is examining combinations of risk factors, such as elevated cholesterol, glucose intolerance, insulin resistance, and obesity, to identify patterns that may presage coronary events. The findings should provide important information for an age group in whom hypertension and high blood cholesterol are quite prevalent and yet are not as strongly associated with the risk of developing cardiovascular disease as in younger people. Significant public health benefits and cost savings are likely as we refine our ability to identify persons who will benefit from medical and lifestyle intervention and focus our efforts and resources where the return will be the greatest.

Evidence of benefits that can result from reducing serum cholesterol levels continues to accumulate. Two recent studies, one using drugs and the other using a combination of strict diet and behavioral changes, reported that lowering cholesterol actually causes regression of atherosclerotic changes in arteries. These results underscore the public health gains to be realized by the National Cholesterol Education Program (NCEP). The NCEP "know your cholesterol number" message is reaching the community: in 1988, 66 percent of adults had their cholesterol levels measured as compared with 35 percent in 1983. The interest of people in knowing their blood cholesterol levels is reflected in increased public cholesterol screenings. To be successful, cholesterol screening must lead ultimately to a reduction in the risk of coronary heart disease (CHD), an objective that can be accomplished only if proper assessment techniques are used and adequate education and follow-up are provided. The NHLBI Recommendations Regarding Public Screening for Measuring Blood Cholesterol have been widely distributed in the expectation that they will improve the quality of public screenings.

One of our primary goals in disease prevention is to facilitate appropriate and early application of current research advances related to heart, lung, and blood diseases and to transfusion medicine. The time between the development of advances in new knowledge and their successful transfer into medical practice and to the public has become remarkably short. Let me tell you about some recent activities that are of immediate benefit to the public health of the United States.

Whenever the Institute undertakes a clinical trial of a drug intervention, it does so with the expectation that the results will lead to improved approaches for management and prevention of disease. However, there are times when a clinical trial demonstrates findings that, while unanticipated, are as important as if the original premise of the study had been confirmed. The Cardiac Arrythmia Suppression Trial was designed to evaluate the effectiveness of three antiarrhythmic drugs in preventing sudden death in heart attack survivors with mild arrhythmias. Last April, use of two of the drugs was halted when it became apparent that death occurred almost twice as frequently among those who took the drugs as among those who took a placebo. Because these drugs had been widely prescribed in the United States for mild arrhythmias, these findings have had a widespread, immediate impact on physician practices. Considerable savings of lives and medical costs should result. This experience underscores the importance of the clinical trial as a research tool which, in this case, revealed that the drug, rather than the disease, was the cause of excess mortality.

Women account for about half of all deaths from CHD in the United States and are twice as likely as men to die in the first few weeks after a heart attack. Attention is now being focused on the mechanisms by which CHD develops and progresses in women. For example, the relative freedom from heart attack experienced by women before menopause has generated investigations of the possible protective effect of hormones produced by the ovaries. Recently, investigators reported that natural menopause tends to lower "good" cholesterol, high density lipoprotein, and raise "bad" cholesterol, low density lipoprotein, but estrogen replacement therapy seems to nullify that effect. The NHLBI's Postmenopausal Estrogen/Progestin Interventions (PEPI) trial is evaluating whether various combinations of estrogen and progestational agents reduce risk factors for heart disease. The results are expected to provide a solid basis for preventive treatment recommendations.

The Institute is also focusing a major effort on risk factor modification in selected populations. The Dietary Intervention Study in Children (DISC) is assessing the efficacy and safety of a cholesterol-lowering diet for prepubescent children who have high cholesterol levels. The NHLBI Growth and Health Study is developing important new information about obesity and its consequences in Black and white preteen and teenage girls. The Lung Health Study for early detection and prevention of chronic obstructive pulmonary disease is the first trial of risk factor modification in lung disease.

Considerable attention also is being directed toward a cluster of 11 southeastern states where the death rates from stroke are so high as to warrant the designation "stroke belt." Of particular interest and concern are the observations that, among Blacks in those states, hypertension is more prevalent, more severe, and less well-controlled, and obesity is more common than among Blacks in other regions. The National High Blood Pressure Education Program has developed a multifaceted stroke belt intervention strategy to address the particular problems associated with hypertension control in the Southeast.

This year has been one of great progress in basic and clinical investigations into the pathogenesis of cystic fibrosis (CF). Discovery of the CF gene has expanded opportunities for understanding the underlying biochemical defect and designing new therapies. Translation of these concepts into improved care for CF patients will require years of investigation. On the immediate horizon, however, is a promising therapy that inhibits excessive sodium and water absorption. Building on the basic science observation that a defect exists in sodium absorption in CF cells, a pilot study of aerosol-administered amiloride demonstrated its ability to thin out airway secretions and slow the disease-induced decline in pulmonary function. If confirmed in large clinical studies, these findings will represent an important contribution to modern CF therapy.

Over the years, I have reported a number of advances resulting from our research program in neonatal respiratory distress syndrome (RDS), and I am happy to report today that a major goal has been achieved. Ever since it was discovered that RDS is caused by a deficiency of surfactant, development of an effective, safe replacement therapy has been a dream of clinicians and basic researchers. In 1989, approval was given for wider use of two experimental surfactant preparations shown effective in improving the course of RDS through clinical studies sponsored by NHLBI. Successful treatment with surfactant replacement is expected to reduce the severity of RDS and need for mechanical ventilation. Long-term follow-up studies are under way to establish the impact of surfactant replacement on the incidence of such complications as bronchopulmonary dysplasia, a serious chronic lung condition that affects 8,000 American newborns each year.

The NHLBI has been a leader in the development of asthma self-management strategies effective in reduction of the frequency and severity of asthma attacks and emergency room visits. Results of our research programs are being widely disseminated through the National Asthma Education Program (NAEP), initiated in 1989 to provide patient, family, professional, and public education about asthma and its management. An NAEP Expert Panel on Management of Asthma has been convened to develop national guidelines for physicians who treat patients with asthma. Improved asthma management is needed particularly for Blacks, who are twice as likely as whites to be hospitalized for asthma and three times as likely to die of asthma. Although corresponding data for Hispanics are not available, a number of barriers to effective asthma management exist, such as low educational and literacy levels and lack of access to continuing health care. In response to this need, the Institute recently announced a new research program to develop interventions that address the special needs of Black and Hispanic children. With this coordinated approach, the Institute hopes to play a major role in the control of asthma by helping individuals learn to manage their chronic disease.

We are pleased to report progress in the quest for improved treatment of two hereditary blood disorders, sickle cell anemia and Cooley's anemia. Scientists have developed transgenic mice whose red blood cells make human hemoglobin. They are now able to implant sickle hemoglobin genes in these animals and cause production of the human hemoglobin S found in patients with sickle cell anemia. These developments bring us far closer to having animal models of this disease to facilitate detailed studies and enhanced exploration of experimental treatments. Researchers studying Cooley's anemia have reported success in the development of oral iron chelators, agents that remove the toxic iron accumulation associated with multiple blood transfusions. Several new agents have now been approved for experimental use and it is hoped that they will prove effective in the management of this chronic disease and eventually replace chelators that must be injected daily. During the past year, the size of the National Bone Marrow Registry, now operating under NHLBI management, doubled to include over 78,000 potential donors. Bone marrow transplantation has become an accepted and effective treatment for an increasing number of diseases of the bone marrow and immune system. Over 270 transplants have been performed as a result of the registry. It is anticipated that improved access to tissue-matched donors and better transplant technology will make bone marrow transplantation an acceptable alternative treatment for severe sickle cell anemia and other serious hematologic disorders.

The National Blood Resource Education Program (NBREP) was formally launched in October 1987 to ensure an adequate and safe blood supply and ensure appropriate transfusion of blood and blood components. In the past year, the program released two major reports providing guidance for health professionals --one on the use of red blood cells, platelets, and fresh frozen plasma and the other on the use of autologous blood. In addition, a mass media public education program was begun to supplement efforts of local blood centers in recruiting blood donors. This year an important program focus will be production of a resource kit for blood banking personnel to improve donor recruitment and retention.

Results of AIDS research have already improved the quality and length of life of patients and helped reduce the spread of the AIDS virus. Clinical researchers have focused much attention on the lung, the organ most affected as a result of HIV infection. NHLBI intramural scientists recently reported finding abnormally reduced levels of glutathione, a natural substance in the body necessary for immune function, in the lungs and blood of men infected with the AIDS virus. An aerosolized form of glutathione has been developed and is now being tested in humans to determine whether it can safely restore the deficiency in the lung. Since glutathione plays an important role in enabling the immune system to function normally, it is hoped that increasing the levels of glutathione will help to prevent AIDS-associated lung infections.

These accomplishments reflect the breadth and depth of our programs of basic and clinical research, clinical trials, and public and professional education. We report them with pride and with confidence that they will provide a foundation for many future improvements in the public health of the United States.

Mr. Chairman, the FY 1991 budget request for the National Heart, Lung, and Blood Institute favors basic research and totals $1,112,502,000. I would be pleased to answer any questions that the Committee may have.

CURRICULUM VITAE

LENFANT, CLAUDE, M.D.
Director, National Heart, Lung,
and Blood Institute, NIH

October 12, 1928, Paris, France

Education: B.S., University of Rennes, France, 1948. M.D., University of Paris, France, 1956.

Professional History: 1957-1958, Research Fellow, University of Buffalo, New York. 1958-1959, Research Fellow, Columbia University, New York. 1959-1960, Assistant Professor of Physiology, University of Lille, France. 1961-1965, Clinical Instructor of Medicine and of Physiology and Biophysics, University of Washington, Seattle. 1966-1967, Clinical Assistant Professor of Medicine and of Physiology and Biophysics, University of Washington, Seattle. 1968-1971, Associate Professor of Medicine and Physiology and Biophysics, University of Washington, Seattle. 1970-1972, Acting Associate Director, Collaborative R&D Program, National Heart and Lung Institute, NIH. 1970-1972, Associate Director for Lung Programs, National Heart and Lung Institute, NIH. 1971-1972, Professor of Medicine and Physiology and Biophysics, University of Washington, Seattle. 1972-1980, Director, Division of Lung Diseases, National Heart, Lung, and Blood Institute, NIH. 1981-1982, Associate Director for International Research, NIH. 1981-1982, Director, Fogarty International Center for Advanced Study in the Health Sciences, NIH. 1982-Present, Director, National Heart, Lung, and Blood Institute, NIH.

Professional Organizations: Association of American Physicians, American Society for Clinical Investigation, American Physiological Society, American Federation for Clinical Research, French Physiological Society, International Federation for Medical Electronics, American Society of Zoologists, Society for Experimental Medicine and Biology, Undersea Medical Society, New York Academy of Science.

Honors, Awards: Thesis Prize, University of Paris, France, 1956. Commendation Tohoku Medical Society, Sendai, Japan, 1973. Superior Service Honor Award, DHHS, 1974. Regents' Professor, University of California, Los Angeles, 1975. Testimonial Dinner, American Thoracic Society, 1979. Honorary Fellow, American College of Chest Physicians, 1979. Honorary

Professor, National Yang-Ming Medical College Taipei, Taiwan, 1980. Honorary Professor, Universidad Peruana Cayetano Heredia, Lima, Peru, 1981. Senior Executive Service Performance Award, 1982. Elected Institute of Medicine, National Academy of Sciences, 1983. American Heart Association Scientific Councils' "Distinguished Achievement Award," 1983. Senior Executive Service Performance Award, 1983. Honorary Fellow Council on Clinical Cardiology - American Heart Association, 1984. Senior Executive Service Performance Award, 1984. Forrest M. Bird Contributory Award, American Respiratory Therapy Foundation, 1985. Senior Executive Service Performance Award, 1985. Presidential Meritorious Executive Rank Award, 1987. Elected Honorary member, Royal Society of Medicine, England, 1988. Honorary Doctor of Science, State University of New York, Buffalo, 1988. Elected member USSR Academy of Medical Sciences, 1988. Cystic Fibrosis Foundation "Breath of Life" Award, 1988.

Authorship, Editorship: Author or Co-Author of 192 scientific publications Served on Editorial Boards of: Am. Journal of Physiology; Journal of Applied Physiology; Respiratory Physiology; Am. Review of Respiratory Disease; Undersea Biomedical Research; Proceedings of Society for Experimental Biology and Medicine; Revue Francaise des Maladies Respiratories; Journal of Applied Physiology; Respiration, Environmental and Exercise Physiology; Am. Journal of Medicine; Continuing Education for Family Physicians; Executive Editor of 40 volume monograph series, Lung Biology in Health and Disease.

Mr. NATCHER. Thank you, Dr. Lenfant.

Mr. Young, I yield to you at this time.

NATIONAL MARROW DONOR REGISTRY

Mr. YOUNG. Mr. Chairman, thank you very much.

Dr. Lenfant, we on this subcommittee are fortunate for the inspirational leadership of our chairman, Bill Natcher, and our Ranking Member, Silvio Conte.

And it's great to be a member of this committee, and it's great to work with people like you and your colleagues who are here today.

As you know because we have met on this subject a number of times, much of my personal time over the last four years has been in the establishment, the funding of, the getting operational the national Bone Marrow Registry.

In the beginning, as you know, we started this using the facilities of the United States Navy, and we funded through the Navy. But our subcommittee directed a little over a year ago that this responsibility would be transferred to the National Institutes of Health and which did happen and you have jurisdiction now for this program.

And from our personal conversations, I know that you are a strong supporter of this, and I wanted to tell you, it's too bad you couldn't make the meeting in St. Petersburg this week because we had the members of the Board were there, we had several young folks who are anxiously awaiting a bone marrow transplant to save their lives.

But as you know in the first year of the Registry, we did about 25 unrelated bone marrow transplantations. This year, three years later, we are doing 25 to 30 each month with a success rate of about 70 percent.

Now, the problem, where we need your help, because the news media has taken renewed interest or a new interest in this program, and because many people are responding favorably, we have a lot of folks who are willing to be typed, but we are sort of overloading the system.

In addition, because the typing has to be so precise, the cost is about $75 per person to have the typing done. I noticed in your budget submission of $4,000,000 for this program, I don't think that any of that includes typing; does it?

Dr. LENFANT. Yes, it does, Mr. Young. There is approximately, five or $600,000 for typing in this budget.

Mr. YOUNG. If we are to create the interest that I think we can, and we started a pilot project in my district last week which we are going to pass on the results to all of our colleagues in the Congress, but the response has been tremendous.

Thousands of people have already told us they would like to be typed. We have gotten a lot of support from industry in our area who are willing to pay for the cost or at least part of the cost of typing.

What do you think would be a reasonable appropriation to you in addition to that $500,000 for strictly for the purpose of typing of donors who cannot afford to pay the $75 themselves?

Dr. LENFANT. Well, the first answer to this question is in effect a question relative to how many names we want to have in the Registry.

As you know, Mr. Young, when the program was created a few years back, the goal was to enter 100,000 individuals into the Registry. Today, because of the successes that you recognized just a moment ago, the goal is to reach 250,000 individuals into the Registry.

Well, as you pointed out, the cost of typing for the first type of the typing is approximately $75 per subject. Thus to go from 100,000, which we have almost reached, to 250,000 individuals represents $11,000,000.

The problem, however, is that that first step of the typing would not allow us to identify good match for individuals in need. It would be necessary to do a second typing, which is called the DR typing.

The cost of that is another $75 per person, and therefore that would add another $11,000,000. So the bottom line, if we say we want to go from 100,000 to 250,000 individuals in the Registry, the cost of typing alone would be in the order of $22,000,000.

Mr. YOUNG. Twenty-two million.

Dr. LENFANT. Yes, sir.

Mr. YOUNG. I think I am on the verge of getting approval to have the military services invited to be part of the program with the support of the Administration, and the Navy, of course, has a laboratory to do much of that typing.

Would you see any problem, either immediately or a problem with having the military budgets be increased somewhat to take care of that part of it, that cost of the typing for the military personnel?

Dr. LENFANT. No, not at all.

I am not aware of the Navy's facilities with regard to this kind of thing, but I am sure that these facilities are quite appropriate, and that everybody would be satisfied with the typing performed in these laboratories.

And so, therefore, I think that that would be a very nice addition to this program. And it would solve, in my views, a great number of problems.

Mr. YOUNG. Let me ask you something, a question that is really bothering me.

One of the young men who was at the meeting in St. Petersburg this week when the Board met was a young black man; and as you know, in checking the Registry, we don't have a lot of ethnic groups or racial groups represented.

And medically from a scientific viewpoint, this young black man is more than likely to find a donor from another black, as a Jewish person is more likely to find a donor from another Jewish person.

Hispanics have the same problem, and my understanding is that even in Hispanics, a Mexican is more likely to find a donor from a Mexican than he would from a Puerto Rican, for example.

Give us some advice or some direction on how do we, how do we aim a recruiting drive to get this message across that we really need participation from ethnic and racial groups in order to have donors for those people who are—if they are going to live, they are going to have to have a donor.

Dr. **Lenfant**. Well, you put your finger on a very important issue, and indeed—I have a bit of competition here.

[Clock is buzzing.]

Dr. **Lenfant**. We have now 89,000 names in the registry. Of these 89,000 names, only 2,600 are from black Americans. And so clearly, it's a very disproportionate ratio between the entire number and the number of minorities. And we have to commit ourselves to increase the number of minorities.

There are several avenues which are being pursued, some by the Board of Directors of the program. In fact, last night, I had a conversation with one of the Directors to explore some of these avenues. One would be to develop some programs in communities where you have a concentration of individuals from groups that you would like to reach.

As you may be aware, Mr. Young, our Institute is very much involved with a number of national programs concerning cardiovascular risk factors. One of them is high blood pressure, and high blood pressure is a problem which is very prevalent and predominant in black Americans. And so what we are thinking about doing, is to use these education programs to communicate some information about the marrow donor programs. We want to use the churches, the schools, the community and TV networks to urge individuals from minority groups to enroll into this Marrow Donor Registry.

It's going to take some time. I have to say it's going to take some resources, but from prior experiences, we know that we will be very successful.

BONE MARROW RESEARCH

Mr. **Young**. Doctor, I have a number of questions that I am going to ask you to just respond to for the record. But let me just say this, in closing, that at the meeting this week of the National Board, Dr. Robert Goode was present, and you know, of course, Dr. Goode, who pioneered the process of bone marrow transplantation some years ago, using sibling donors.

And he reported to the Board that as of now, he and his colleagues have determined that some 60 types of diseases may successfully be treated by bone marrow transplantation. And that is pretty exciting when we realize that the success rate is about 70 percent, considering that the patient was terminal without the transplant.

What do you see as the future of medical research from your standpoint at NIH on the question of how bone marrow transplantation might fit into other types of disease or other types of cures?

Dr. **Lenfant**. Well, I am extremely optimistic. I should say in a word that the reason why our Institute was so interested in assuming a responsibility for the Registry is that we saw in it an opportunity for new research avenues which would span from basic to clinical research and would be of benefit to a great number of our programs. Not least is the one that was discussed here earlier this morning by Dr. Broder who spoke extensively about gene transfer and gene therapy, an activity in which we are a dominant partner. This activity is going to be greatly helped by the research that we can do relative to bone marrow biology and bone marrow transplantation.

I think that there are many, many research opportunities which have been untouched as yet with regard to this area of biology. I am absolutely confident that once we will have addressed these research avenues and pursue them successfully, instead of doing about 25 transplantations a month, as you stated earlier, I can see the time when it will be up to 100 cases a month and even more.

We should not forget that in this country alone in a not so distant future there may be a need for up to eight to 10,000 bone marrow transplantations per year.

Today we are doing about a couple of hundred a year, so we have a long way to go to achieve this goal. But that will not be until we have addressed these research avenues which are so many. I will be pleased to put them in the record in great detail.

I know we are pressed for time.

[The information follows:]

BONE MARROW TRANSPLANTATION RESEARCH OPPORTUNITIES

Bone marrow transplantation is an effective and accepted therapy for an increasing number of diseases of the bone marrow and the immune system. Bone marrow transplants differ from most tissue or organ transplants in that bone marrow contains cells with an ability to develop immune responses. Although the field of bone marrow transplantation has been developing rapidly, many opportunities remain.

Much research needs to be done to improve the results of bone marrow transplantation from donors. The four major problems in marrow transplantation are 1) graft failure, either early (primary) or late (secondary); 2) reaction of the transplanted marrow against the recipient (graft-vs-host disease); 3) stimulation or maintenance of graft-vs-leukemia effect, when the purpose of the transplant is to treat leukemia; and 4) cost and laboratory capacity for HLA typing of donors.

Basic research is needed to isolate and culture primitive stem cells, the precursors of all blood cells, in order to learn more about their basic biology and responses to various new growth factors. These studies will help improve the success of bone marrow grafts. This basic research may also lead to the harvesting of these cells from the blood where they circulate in small numbers. "Marrow" donation could then consist of an apheresis procedure, done in a few hours, obviating the need for hospitalization, general or spinal anesthesia, and time in an operating room. Growing large numbers of these cells in test tubes could improve the chances for a successful graft and speed the recovery of marrow function. Further development of techniques to grow and especially to preserve stem cells will permit marrow or peripheral stem cells to be harvested before the patient-recipient's bone marrow is destroyed. Stem cells are found in relatively large numbers in umbilical cord blood, most of which is now discarded. It is possible that umbilical cord stem cells could cause fewer complications when transplanted, so that HLA matching need not be so exact. If so, a bank could be established where HLA typed stem cells are frozen, to be used as a transplant when needed. Most of these studies must be done on blood or marrow from donors, with later testing in marrow recipients.

Additional research is needed on the factors influencing the occurrence of graft-vs-host disease, which causes major morbidity and mortality in the bone marrow recipient. It is important to learn whether the factors that influence the occurrence of the beneficial anti-leukemic (graft-vs-leukemia) effect are related to those that produce graft-vs-host disease. The relationship of these phenomena to HLA types and matches and the immunologic events involved in their expression need to be delineated. Reducing T-cells (one kind of white blood cell) in marrow to be grafted seems to reduce the frequency and severity of graft-vs-host disease, but only at the cost of diminishing the likelihood of a successful graft and the beneficial graft-vs-leukemia effect. Additional research may overcome some of these problems. Clinical trials are needed to evaluate the results obtained with different T-cell depletion techniques and to compare T-cell depletion with other approaches to the control of graft-vs-host disease. This research may ultimately lead to better graft success rates, reduced or eliminated graft-vs-host disease, and enhanced preservation of the graft-vs-leukemia effect, where desirable.

Methods for HLA typing need to be refined and automated, where possible, to improve test reliability and increase laboratory volume. New methods of HLA typing need to be developed to define the subtle differences in donor and recipient types that remain undetected using the present technology, and may result in graft rejection and graft versus host disease. Further, results from these new techniques must be compared with those from standard serological procedures. The NMDP repository of cells for donor-recipient pairs will be invaluable for these studies. This research will permit faster and more accurate HLA typing, especially for minorities where current techniques are often inadequate. It will also permit separation of clinically important molecular differences from those of little or no importance, permitting careful matching for the former and little concern for the latter. Controlled clinical trials will be needed to confirm the experimental results.

The NHLBI plans to establish a clinical bone marrow transplant (BMT) unit in the NIH Clinical Center. The availability of a dedicated facility for BMT would enable intramural scientists to extend findings from their basic research laboratories and attempt innovative, experimental, therapeutic interventions for specific diseases. The possibility of treating genetic diseases through modifying the genome of somatic cells by gene insertion seems likely to be achieved in the next several years. It is probable that such experimental treatment will occur initially in the context of BMT. The development of a BMT facility at the Clinical Center will enable intramural scientists to assume a leading role in the development of such BMT applications. Most of the published clinical research in bone marrow transplantation has relied upon historical or previously published studies for patient comparison groups. Although information derived from such studies can be useful, contemporary comparisons will be needed before conclusions can be regarded as firm. The intramural bone marrow transplant program may be able to stimulate such controlled clinical research through leadership and example.

The NHLBI will expand its National Blood Resource Education Program (NBREP) to include public and professional education about BMT. Considerable media attention has been given to the plight of individual patients for whom donors are difficult to find, and a number of patient-focuses, crisis donor recruitment drives have been undertaken. Measure need to be taken to ensure that prospective donors provide informed consent and meet certain requisite health criteria, and that samples are collected properly and efficiently. Give the prospects for expanded interest in bone marrow donation, an educational effort is essential to address these needs. NBREP will especially focus on educating minorities to the needs for marrow donors to make the program a resource for all Americans.

Mr. YOUNG. I wish you would do that because I know that you have established a special research program with NIH for this program, and we appreciate that.

I appreciate all the time that you and I get to spend together on this really exciting subject.

Dr. LENFANT. Thank you.

I should say that we are planning to establish this research program at NIH. We are realigning some of our activities so that we can develop this research program on bone marrow biology and transplantation.

I am confident that we will be able to do it. I see a great potential for the future, and we really are committed to exploring it to the fullest.

Mr. YOUNG. It's exciting; isn't it?

Dr. LENFANT. Yes, indeed.

Mr. NATCHER. The committee will now recess until 2 o'clock.

[Recess.]

ACHIEVEMENTS IN HEART, LUNG, AND BLOOD RESEARCH

Mr. NATCHER. Doctor, your long-term advances are an example of what makes us proud of the National Institutes, but we also need to maintain this momentum. I think you would agree with that.

Can you give us one or two examples of what the institute has done for us in the last year?

Tell us something that we can talk about.

Doctor, you have a good story. We want you to start telling it right now, doctor, if you will. We are going to listen to you.

Dr. LENFANT. Mr. Chairman, I would like to tell you about two new events which I believe will be of great benefit to the American people.

One of them relates to a heart disease called hypertrophic cardiomyopathy. This disease has been in the news lately because of the sudden death of a basketball player on the West Coast.

The reason why I have pinpointed this condition is that during this year, a marker for the gene responsible for this condition has been identified.

Indeed, hypertrophic cardiomyopathy is a genetically determined disease.

Having identified a marker for this condition is going to lead to very significant advances. The interest with this condition is that it is a relatively prevalent condition.

Unfortunately, often its outcome is as dramatic as what we have seen during the last few weeks in the sense that it is not identified, not recognized before the sudden death of young men and women often on the occasion of a sport activity.

So, here is a scientific advance which is extremely significant.

As we progress in our research on this condition I think that we are going to have a great deal of impact on public health.

The second event that I would like to mention relates to one condition that I have spoken about in previous years, but this year something very important has happened. This condition is called respiratory distress syndrome of the newborn.

Over the years I have told you that we have made considerable advances to reduce mortality and morbidity of this condition, but we still have a group of premature born infants, with a very low weight who as yet can not be treated in a satisfactory fashion.

Through research, the cause of this condition has been found to be due to the absence of a material called surfactant which is normally produced by the lungs but which is absent in this condition. After years of research, surfactant is now synthesized or can be extracted from animal lungs. This year the Food and Drug Administration has allowed the use of these nonhuman surfactants in clinical trials to assess their efficacy. This gives us the possibility to further advance the treatment of this condition, which affects a great number of premature born infants.

These are two advances which I think are very significant. They will eventually lead to an effective treatment of these two conditions.

APPROPRIATIONS

Mr. NATCHER. Doctor, after subtracting Gramm-Rudman cuts and other taps, how does your 1990 appropriation compare to 1989 and to the President's request for 1990?

Dr. LENFANT. In 1989, the appropriations of the Institute was $1,045,985,000. In 1990, after the subtraction that you just mentioned, including the other taps you mentioned the appropriation left to the Institute is $1,062,268,000. This amount compares to the 1990 President's Budget amount of $1,082,497,000.

This year the President's budget is $1,112,000,000.

AWARD RATES

Mr. NATCHER. The Heart Institute is experiencing one of the largest declines among the institutes in numbers of competing grants during 1990.

As you know, doctor, the number of new awards drops from 698 to 601 and then rebounds and comes back up to 718 in 1991. How disruptive is this to your research?

Dr. LENFANT. I believe, and so do the members of our National Advisory Council, that it is a very disrupting situation. Not only does it affect the research programs themselves and the progress that we can make, but I think it has a very negative impact on the scientific community, particularly among young individuals who are considering whether they are going to enter a research career or do something else.

This up and down situation, up and down and up and down again deters them, I believe, from going into research.

INTRAMURAL RESEARCH BUDGET INCREASE

Mr. NATCHER. The 1991 budget includes an overall increase, as you know, for your institute, doctor, of about 4 percent. Within this total, however, your in-house research would receive over a 9 percent increase.

This is a cumulative increase for your own labs of 20 percent in two years. Have you made a deliberate decision to expand this work as a higher priority than your extramural work, Doctor?

Dr. **Lenfant**. Yes, Mr. Chairman. There are a number of reasons for this increase. One of the important reasons is that if we look back over the past years, you will see that our Institute has had a very small increase for its intramural research program. We feel there is a great deal of catching up to do.

In addition, there are some specific allocations of the increase you are mentioning. A fairly large portion is going to be allocated to the management fund of the intramural program research, namely, to the cost of the infrastructure of the intramural programs in the clinical center.

In addition, some funds have been put aside for the continuation and further development of the Cardiac Energetics Laboratory, which you may recall was recently created and for which this Committee gave a special appropriations to buy the necessary equipment.

I should also say that we have a sizeable increase in our intramural AIDS research program; it is in the order of $2 million plus.

Finally, as was mentioned this morning, we intend to start a bone marrow transplantation program as well as further developing our gene therapy program. As you heard this morning, this is done jointly with the Cancer Institute.

CARDIAC SURGERY UNIT

Mr. **Natcher**. The committee has been approached by a number of individuals, Doctor, who are concerned about the decision to close your heart surgery unit. You wrote the committee about this last month. We will insert that letter in the record at this point.

[The information follows:]

January 30, 1990

The Honorable William H. Natcher
Chairman, Subcommittee on Labor, Health and Human Services,
Education and Related Agencies
House of Representatives
Washington, D.C. 20515

Dear Mr. Chairman:

In preparation for the upcoming FY 1991 appropriations hearings, I recently met with Mr. Mike Stevens and Mr. Mike Hall to review with them topical issues and policy concerns pertinent to the hearings. One of the topics that we discussed concerned important changes in our intramural research program; specifically the phasing out of cardiac surgery services at the Clinical Center and increased emphases in other areas of our clinical research program. Because of your continuing interest and support of Heart, Lung and Blood research programs, it was suggested that I write to inform you of these significant developments. I am also sending Senator Tom Harkin a letter identical to this one.

For many years the National Heart, Lung, and Blood Institute (NHLBI) has maintained a cardiac surgery unit within its Division of Intramural Research to support the cardiology research program. After considerable deliberation, it was determined to be in the best interest of the government, and, the intramural research program, to phase out the NHLBI Cardiac Surgery Branch and procure surgical support off-site. This decision was made by me, as Director for the Institute, after advice and recommendations from the Director, Division of Intramural Research, the appropriate Clinical Branch Chiefs, and senior staff of the Institute. This was also discussed with the Acting Director, NIH and the Assistant Secretary for Health, who have supported this decision.

The decision to phase out the Cardiac Surgery Branch was based on three major factors: (a) the changing nature of the cardiology research program; (b) the inability of the Federal Government to recruit and maintain a permanent cadre of qualified cardiac surgeons; and (c) the need to meet program priorities within budget constraints.

a. Changing nature of the cardiology research program

From an historical perspective, the NHLBI Cardiac Surgery Branch has made outstanding contributions to the fields of clinical surgery and surgery research. This was especially true in the areas of valve replacement procedures and hypertrophic cardiomyopathy. Cardiac surgery has always been essential and integral to the Institute's Cardiology Branch research program in providing an emergency back-up for invasive cardiology research procedures such as angioplasties.

However, currently the field of cardiology and cardiac surgery has advanced to the point that many of these procedures have now been accepted as standard clinical practice. The research of the Cardiology Branch is now evolving from purely clinical approaches involving invasive cardiology to new, molecular biology approaches for the treatment of cardiac disease. For these reasons the Institute's intramural invasive cardiology research program is being completely phased out, and no more angioplasties will be performed at the NIH Clinical Center.

As a result of these changes in the cardiac research program, the number of patients requiring cardiac surgery is expected to decrease significantly. Last year there were approximately 200 cardiac surgery patients. We expect about 155 patients this year with about a 30 percent or more decrease expected over the next year or two. The majority of the patients requiring cardiac surgery in the future will not be involved in ongoing research protocols, but will be former patients in need of clinical service such as valve replacements or coronary artery surgery. This routine clinical care can be performed at almost any hospital with a surgical facility. A small group of patients, approximately 50 per year, will be part of an ongoing hypertrophic cardiomyopathy research protocol.

b. Inability to recruit and maintain a permanent cadre of qualified surgeons

Currently, there are only two operating surgeons on board, one of whom will retire in February 1990. While there is an excellent group of 2-year surgery associates on board, it has become increasingly difficult to recruit a permanent cadre of qualified surgeons. One reason is the limited volume and nature of the surgery to be performed. Another is that the Federal pay scale cannot begin to compete with the pay scale of private hospitals and the potential earnings from private practice for board certified cardiac surgeons. Thus without the assurance of being able to recruit and retain senior surgeons, it is not possible to carry out a viable surgery unit to support cardiology research.

c. Program priorities and budget constraints

The clinical program of the NHLBI requires the commitment of a significant portion of the Institute's intramural resources. The hospital support costs for activities such as nursing support, critical care medicine, anesthesiology, pharmaceutical, and diagnostic radiology and nuclear medicine totaled approximately $27 million in FY 1989. More than one-third of this amount, about $10 million, was directly attributable to the maintenance of the cardiac surgery program. Given the changing nature of the cardiac

> research program, the relatively small number of patients and limited types of cardiac surgery being performed, and the resource needs of other intramural research programs, the NHLBI can no longer justify this level of support.

In the past year, the NHLBI has made extraordinary advances in the intramural research program and we are now faced with the challenge of moving these advances to the bedside by enhancing our clinical research program. This year has seen the emergence of gene therapy and gene transfer technology as a national health research priority. NHLBI scientists have successfully completed the first genetic transfer in humans in history, and expanded clinical trials are needed now so that this technology can ultimately be available to treat thousands of patients with genetic and non-genetic diseases.

Closely related to this is the need for a bone marrow transplantation unit in the Clinical Center. NHLBI is already responsible for the National Bone Marrow Donor Program. As part of our Blood Resources Education Program, we have initiated an education program for bone marrow transplantation to increase understanding of this program and improve donor recruitment. The transplantation unit in the Clinical Center is needed to enhance our research effort so that this therapy may be available to wider spectrum of diseases. The transplant unit will be initiated as part of the expansion of our clinical hematology program. In addition, research is needed to develop alternative serological tests and new molecular testing methodology to help increase the number of minorities in the donor pool.

Another important clinical initiative is in the area of Cardiac Energetics. As a result of funds provided in FY 1989 appropriation, a new facility will soon be completed, and important clinical studies will be initiated to help us understand how the heart actually functions at the cellular and molecular level. This knowledge will lead to new, noninvasive diagnostic and advanced new treatment methodologies.

The decision to phase out on-site cardiac surgery will allow the redirection of finite resources to support these new, high priority clinical research programs.

NHLBI is currently in the process of establishing an agreement for surgical services with one or more of the leading facilities in the Washington, D.C. area. This arrangement will permit us to continue to provide the finest quality care for those cardiac patients that might require surgery as part of their follow-up care and for emergencies. A close working relationship between our physicians and the surgeons at the local hospital will ensure consistent care of the highest quality. The actual closing of the cardiac surgery services in the Clinical Center is planned for July 1, 1990.

We are making every possible effort to make this a smooth transition and to ensure the best possible care for our cardiac patients. We will continue to evaluate patients in the Cardiology Branch and provide medical treatment at the Clinical Center. We will also continue the outpatient clinic for patients who have had cardiac surgery.

I hope this information is helpful and I will be pleased to provide any further information. I want to take this opportunity to again express our appreciation for your continuing interest and support of the NHLBI research programs.

Sincerely yours,

Claude Lenfant, M.D.
Director

Mr. NATCHER. Briefly, Doctor, review for us why this decision was made and tell us how much money is involved.

Dr. LENFANT. The reasons for this decision are complex and many.

The first reason that I should like to mention is that when the Institute's cardiac surgery program started many years ago, it was really the pioneering phase of cardiac surgery. Today in this city alone there must be five or six teams doing cardiac surgery.

Therefore, our program no longer has the character of uniqueness that it had many years ago. Within this context, the Institute has established new priorities in our intramural programs. For example, the gene transfer and gene therapy programs and the transplantation program that I just mentioned are amongst our highest priorities.

In addition to that, we have within our ongoing intramural activities a number of competing needs. For example, in our medical cardiology program we are initiating research avenues which involve new approaches in technologies such as molecular and cell biology and biochemistry and for which we have to find the resources within our budget.

Another reason that I would like to mention has to do with finding a replacement for one of our two cardiac surgeons who is retiring.

As was discussed yesterday, the salary structure for some medical sub-specialities is just not competitive. One such speciality is cardiac surgery. A cardiac surgeon here in town would probably make very easily between $200,000 and $300,000 a year.

As you heard, the maximum salary that we can pay is just over $100,000. Until a month ago we have had two operating surgeons. One of them retired, and we were, therefore, left with only one. Of course, we cannot have a cardiac surgery program with only one surgeon. We have looked for a new surgeon to come into our program. Although we did identify a couple of individuals who might have qualified for this position, they made it clear that they did not view that as a lifetime position because of the limitation in income.

If we need to recruit for new cardiac surgeons relatively frequently, we feel it would be very difficult to sustain the type of quality program which we want to have.

Mr. NATCHER. Mr. Conte, I yield.

Mr. CONTE. Thank you, Mr. Chairman.

Dr. Lenfant, I want to welcome you back to our committee once again. I always sit here and enjoy your presentation because I learn so much about medicine from you.

You have been before us many, many times. The Chairman and I ought to be getting our M.D.'s from you, Dr. Natcher and Dr. Conte, and Dr. Stokes, too.

Mr. Chairman, we could go and practice together.

Dr. LENFANT. We have good jobs within our Institute.

COOLEY'S ANEMIA

Mr. CONTE. You know Cooley's Anemia is a major disease which strikes many Americans especially of Mediterranean heritage. What is your current funding of Cooley's Anemia research?

Dr. LENFANT. Until a few days ago it was $8,700,000. Just a few days ago we were able to award some additional grants researching Cooley's Anemia. That has raised the amount by about $500,000 or $600,000.

Mr. CONTE. What is the current and potential future treatments involved in Cooley's Anemia?

Dr. LENFANT. I think it is very good.

I think it is very good because there are several avenues which are pursued, one which is a short-term avenue with immediate application.

It is the development of iron chelators. They are compounds which remove excess deposits of iron from organs in the body. Excess iron deposits are coming from the great number of blood transfusions that these patients must receive to compensate for their anemia.

Today there are compounds to remove this iron excess, but the administration is complex. Therefore the compliance is very poor. Lot's of work is going on to develop new iron chelators. These grants which I just mentioned now are grants to develop new oral chelators.

This is a research avenue which has the potential for immediate impact. I can tell you because I speak to many families of young patients with Cooley's Anemia there is nothing that they would welcome as much as to see a very efficient oral iron chelator being developed because it would greatly help their children and would assure the compliance to the therapy and, therefore, prolong the lives of these young people.

The two other avenues which I would like to mention will have an impact in the future, but we think that they are very important to pursue at this time. One avenue is genetic therapy which was explained to you this morning when you asked what is genetic therapy. In this particular case it would be to insert into cells of patients with Cooley's anemia a gene that would reinstate the production of normal hemoglobin instead of having the abnormal hemoglobin responsible for the condition.

The potential is real. I would say within a few years from now we can expect that gene therapy may be possible.

The third avenue which I would like to mention is that of bone marrow transplantation. This condition Cooley's anemia results from an abnormal hemoglobin. What we are talking about by bone marrow transplantation is basically to transplant into these patients normal red cell precursors which could grow and multiply and replace the abnormal cells which are produced in this disease. I think the prospects are very good. The thing which, in my opinion, is very exciting to researchers is that there are ideas to approach this disease, and basically what we have to do is just get to it.

Mr. CONTE. That is encouraging news.

In your professional judgment, how much should we be spending on Cooley's Anemia research?

Dr. LENFANT. I think the iron oral chelator development which I mentioned is soon to be followed by clinical work, to test the efficiency of the new compounds. In addition, according to my professional judgment, there should also be more resources for the two other avenues which I mentioned, bone marrow transplantation and genetic therapy.

We could speed up the process, getting to satisfactory results faster.

Mr. CONTE. You say chelators play a very important role in the treatment of this disease, iron chelators does your Institute have any plans to investigate the use of the iron chelators and other possible therapy?

Dr. LENFANT. Yes. We will move into the clinical testing of these compounds as soon as the lack of toxicity has been established. We are ready to do it. The research to develop the compounds is progressing very well.

As soon as they come out from the laboratory, we are ready to move to clinical trials to demonstrate the efficacy of this product.

NATIONAL ASTHMA EDUCATION PROGRAM

Mr. CONTE. I understand that you are working with the School of Health and Education Program at the Department of Education to improve awareness of asthma among school children.

Can you review for us what activities you are involved with?

Dr. LENFANT. Well, asthma is a very prevalent disease. We are talking about 10 million people in this country, but there is an uneven distribution among the population. There are two groups in the U.S. population which are particularly affected by this condition. First, in our young people, that are less than 18 years old, there is a higher prevalence of this disease. Second, there is also a higher prevalence in minorities, particularly blacks. In fact, it is probably twice as prevalent in blacks as it is in whites.

Asthma is a disease that very few people should suffer from. They may have it, but they could be treated provided that they know how to treat it.

One of the sites where asthma occurs or where it is exacerbated is the school environment. As I said, this disease is very prevalent in youngsters.

The problem we have is that often the schools are not equipped to address asthma exacerbations when they occur. There may or may not be nurses. The nurses may or may not know what to do.

The school faculty itself may not be prepared to deal with a kid who is short of breath all of a sudden. It is quite a scary site to see youngsters not able to breathe. Yet, all these situations could be handled in a way where they could take care of these youngsters very effectively. To address this issue, we have a National Asthma Education Program. One of its targets for action is the school environment.

The best way to get access to the school environment was, of course, to go to the Department of Education.

I have met with officials in the Department of Education to discuss our program and they have indicated their wish to collaborate with us. However, their system seems to be more complicated than ours, but I know they will work with us. I will be discussing this collaboration with them again to see how best we can do it.

It is interesting that you asked that question.

I see here the logo of the Department of Education, and one of the simple things that I have asked the Department of Education is their permission to put their logo as well as ours on the materials we would distribute to schools to make it very official and to gain more acceptance in the schools.

One of the topics of discussion is whether we are going to get the approval to reproduce the logo. I am confident we will be able to do it.

Mr. CONTE. My time is up.

Thank you, Mr. Chairman.

Mr. NATCHER. Mr. Stokes?

FRAMINGHAM HEART STUDY

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Lenfant, it is always a pleasure to have you back before our subcommittee and have the chance to talk with you.

In your formal statement you mentioned the Framingham Heart Study which you tell us recently reported results of echo-cardiographic studies that revealed increased left ventricle mass to be a powerful predictor of future heart problems in blacks and in elderly persons.

Can you tell us a little more about this.

Dr. LENFANT. Yes, Mr. Stokes. That is a very interesting and significant observation. I should tell you at the outset that this observation was made by one of our very distinguished scientists, who unfortunately died prematurely in a tragic way just a few weeks ago.

You might be interested to know that next Thursday I am going to the Convention of the Association of Black Cardiologists. I feel very privileged to have been asked to deliver the first lecture named after him.

When he was working in our Institute at Framingham, he did, indeed, note that, particularly in blacks and other minorities, there is a very high prevalence of thickening of the left ventricle wall of the heart. When this thickening was observed, often you would see in subsequent years the occurrence of heart disease, particularly high blood pressure and, congestive heart disease. It is a very interesting observation, and echocardiography is now actually being used in many large studies in order to confirm this observation.

I think it may have the potential to help us to detect individuals who might be at greater risk of some cardiovascular disorders.

ASTHMA

Mr. STOKES. The doctor you referred to, Dr. Daniel Savage, was a very distinguished physician.

Dr. Lenfant, you stated that blacks are twice as likely to be hospitalized for asthma and three times as likely to die of asthma. Tell us why this is.

Dr. LENFANT. It is really very difficult to know. I think all experts agree with your statement. One of the main reasons may be that of access to care.

There is some emerging evidence to confirm that hypothesis. There may be some other reasons which are of biological or physiological nature.

But, I think most people would agree at this point in time that the most compelling reason may be that of access to care.

In fact, we are addressing this very issue, by way of a research program which is being initiated very soon. It will assess the access to care and which intervention would be most suitable to take care of these patients once they have been recognized.

Here again, we see opportunities to make very substantial progress and, hopefully, to reduce this morbidity that you are referring to.

Mr. STOKES. You also told us that data on asthma among Hispanics is not available. How do we account for that? Here in 1990 you don't have any such data?

Dr. LENFANT. Well, I wish I could answer this question. I can't, but I can tell you that it is going to change.

The reason why I am telling you this is that the National Center for Health Statistics has performed last year and the year before a national health survey which was specifically directed to the Hispanic American.

Therefore, from this survey this data will emerge. Perhaps next year I will be able to give you a better answer.

BONE MARROW TRANSPLANTATION

Mr. STOKES. I certainly hope so.

We read a lot now and hear a lot about bone marrow transplantation. What diseases can be effectively treated with bone marrow transplantation?

Dr. LENFANT. Several. At the present time in the United States, bone marrow is essentially used for treatment of different forms of leukemia. This is a blood cancer, if you will. But, it can be used for other conditions such as hereditary immune deficiency and hereditary anemia.

Of course, it could also be used for hereditary blood diseases such as Sickle Cell disease or Cooley's Anemia, as we were talking about just a few moments ago.

Mr. STOKES. How will the Institute increase the number of donors, especially among ethnic minority donors?

Dr. LENFANT. Well, Mr. Stokes, I think you know that the National Marrow Donor Program was transferred to our Institute just about a year ago.

I should tell you that during this period of time we have been able to increase the number of donors from 37,000 to 89,000. I am embarrassed to tell you that from this number the number of minorities is very low.

Indeed, we have only 2,600 blacks who are registered in this registry out of the 89,000. We know we have a problem, and we are going to address it.

We are going to address it by special education programs directed to minority communities. We are also going to use some of the other conduits that we have as for example a program on high blood pressure education in blacks. As we speak about high blood pressure we will also encourage blacks to register for bone marrow donations at the same time.

I wish I could tell you better news, and I wish I could tell you next year I will have 50,000 blacks registered. All I can tell you today is we are going to do the best we can to achieve this number, whatever number we can reach. But, I am not sure that it will ever be a big enough number.

Mr. STOKES. Let me ask this, Doctor. Do you feel that maintaining the bone marrow registry as a national health service is consistent with your mission as a research agency?

Dr. LENFANT. Yes, I do. I do for the reason I was mentioning this morning.

Clearly, it is now, more of a service function than anything else. But what this service function does to us, is to give us access to a very unique clinical material.

Now, bone marrow biology and bone marrow transplantation and the medicine of bone marrow are really in a developmental stage. For these areas to mature we have to be able to have access to the clinical material being developed.

What I see for us in running this registry is, first, the access to this clinical materials but also the ability to initiate research programs which will span from very basic research to clinical research.

Basically, it will mean improving the technology and making this technology much more available.

SICKLE CELL RESEARCH CENTERS

Mr. STOKES. Doctor, let me ask you about the Sickle Cell Centers. Are they in danger of being reduced in 1991? What is your request for 1991?

Dr. LENFANT. Mr. Stokes, one of the most difficult problems today is that of our centers program. As you know, our Institute supports 64 centers. Ten of them are Sickle Cell centers.

As you probably know because of competing needs the budget allocated to the centers, all of the 64 centers, has been level for four or five years.

The result is that we are compelled to impose more reductions each year to the centers. This year, for example, the reduction is in the order of 20 to 22 percent. This impacts on the work done in these centers.

The solution that we have to this problem is to cut the number of centers unless there is a possibility to reallocate more funds to this program. But at the present time I do not see this possibility. Therefore, the solution is to cut the number of centers in order to allow each remaining centers to be appropriately funded. We cannot cut the number of Sickle Cell centers because we must have 10 by law. Therefore, the reduction will be in the other activities. I think this is going to create a number of problems and pressures on the Institute also.

The bottom line, to answer your question is that we will not cut the number of Sickle Cell Centers, but it is very possible that the amount awarded will be very significantly reduced.

Mr. STOKES. Thank you, Doctor.

Thank you, Mr. Chairman.

Mr. NATCHER. Yes.

Mr. Pursell?

HEALTH PROMOTION AND DISEASE PREVENTION

Mr. PURSELL. Thank you, Mr. Chairman.

In the general field of heart, lung, a lot of doctors that I have had some discussions with are looking at physical therapists, looking at the physiologists. I guess you are on a couple of boards, according to your resume, journal boards.

You see a lot of exercise programs, new clinics revising, corporate clinics being developed. The country is jogging, power walking, bicycling, swimming, exercising.

I have read 78 pages of this budget from your department and I don't see the word "exercise" anywhere.

Is there a reason for that?

Dr. LENFANT. You saw many other words such as prevention. Prevention, Mr. Pursell, is not just one thing. It is a number of things.

Mr. PURSELL. Well, would it be like a good dietary program with an exercise program? I don't see that here in the budget. Maybe I missed it.

Dr. LENFANT. First of all, in the budget as it is constructed now, there is not a line in the budget that says prevention programs.

Mr. PURSELL. I understand that.

Dr. LENFANT. It is kind of woven, if you want, throughout the budget.

Mr. PURSELL. Couldn't we find one line that says "exercise" that would reduce heart cardiovascular disease? Maybe I am listening to the wrong people out there. The whole country is exercising, and so on.

I saw a school system spend $1 million, elementary, secondary, a large school system in the system in the State of Michigan put $1 million in an exercise and nutritional program for the students and the faculty.

Dr. LENFANT. I am sorry the word "exercise" is not in our budget justification. I can assure you in our Institute there is an absolute unqualified commitment to disease prevention and, hence, health promotion.

As part of that is exercise. Our Institute is supporting research on the efficacy of exercise and other healthy habits as preventive regimens.

I can assure you that exercise is part of our program and that we have a great concern to promote and foster good health habits among the American people.

Mr. PURSELL. If you are looking at the Health and Human Services structure departmental-wide, and you look at the National Institutes of Health, it seems like structurally we are doing all right in biomedical science and basic research. I think you are performing very well.

It seems like there is a piece of this whole reduction of diseases through good nutritional programs that should start in the early ages. We are putting $.5 billion into Head Start, and our health component in elementary schools is probably one of the lowest priorities in the country.

In my school system they don't even have nurses there, let alone gym teachers. A lot of teachers don't feel qualified to teach a curriculum that has good exercise programs outside of recess and what kids do in little leagues after school.

I am not saying it has to be a curriculum-oriented structure. I know I am getting away from your basic budgetary request before this committee.

It seems to me that you are in a national role of focusing this nation, Dr. Sullivan and the Surgeon, new Surgeon General, that there ought to be major national emphasis on the combination of good nutrition and good exercise with no smoking.

Dr. Sullivan has now articulated that very well. Here is one of the best atheletes in the country sitting right here, the Chairman of this committee and another one sitting down there. I don't know about Bernie.

Mr. **Early**. Didn't play anything.

Mr. **Pursell**. Joe Early was a great athlete and works out every day. I think we are missing something here, especially in an area like you have.

DEMONSTRATION AND EDUCATION RESEARCH

Dr. **Lenfant**. Sir, I am sorry that we have not been able to articulate it in an effective way. The fact of the matter is that our Institute now is supporting, I think, close to $10 million a year of demonstration research projects.

On the one hand these projects are to assess how early you can teach children in school to develop good healthy habits, and on the other hand to maintain these good habits by further education curricula in school.

Excuse me, Mr. Pursell, you are from the State of Michigan? I think that actually we have one such program in Michigan.

Mr. **Pursell**. I can remember 10 years ago a study done by a Dr. Tom Gilliam at the University of Michigan in the fourth grade. Now, he was not a scientist. He was in the physical education department.

He did a study in the fourth grade on nutrition and dietary curriculum change in the fourth grade compared to other controlled classes out in the Saline Elementary School System.

Those kids changed their eating habits, went home, told their parents to lay off the ice cream and cake and potato chips and all that, and changed the behavior of that fourth grade class for the rest of their life. That study was done by the NIH.

It may be your department. I am going to go and pull it and see what department it came out of.

It was a very exciting study for some of us who are trying to find out why we aren't emphasizing this. That study laid on the shelf. The school system didn't pick it up.

We lose track of some interesting, exciting changes of behavior that would bring down heart disease, cardiovascular problems.

Dr. LENFANT. With your permission, I would like to send you a description of the programs that we have. I am sure you would find them resembling the study Dr. Gilliam did 10 years ago.

Once again, we are very strong advocates of health promotion and prevention education. The earliest you do it, the better off you will be. We do believe indeed that to work in the school environment is the way to go with that.

As I was saying with reference to asthma a few moments ago, if you want to get access to the school environment, you have got to have the help of the Department of Education.

Mr. PURSELL. At the local level.

Dr. LENFANT. This is hard at the local level.

[The information follows:]

DISEASE PREVENTION AND HEALTH PROMOTION IN CHILDREN

The NHLBI is currently funding several studies aimed at disease prevention and health promotion for children. The goal is to develop and evaluate programs that teach healthy behaviors such as good eating habits, regular exercise, and abstinence from drugs and smoking. These programs are often aimed at controlling other risk factors for heart disease such as blood pressure and blood cholesterol levels. Five initiatives are described below.

School-Based Demonstration and Education Research: The NHLBI currently funds a number of school-based cardiovascular risk reduction studies that are categorized as demonstration and education research. Research teams reflecting a variety of backgrounds address one or more of the following risk factors: nutrition, exercise, smoking, high blood pressure, and stress.

The impact of the programs are being measured using knowledge, attitudes, behavior, and physiological criteria. Several of the studies focus on making changes in school policy and procedures that will lead to changes in the content and preparation of food served by the school cafeteria. Increasing and improving physical activity opportunities for children are the goals of other programs. Some of the projects have a family or parent component in which the parents participate in changing the home environment as well. Racial and ethnic minorities are well represented in the study populations. Several new studies address the effectiveness of training teachers so that they can influence student behavior regarding risk factors for cardiovascular disease.

Several of these studies were completed in 1988. A national conference was held in September 1988, to report the findings of ten of the studies, and recommendations were made regarding technology transfer efforts to disseminate the research results and the curricula from the studies. A paper summarizing the ten studies and an article on each study were published in the Summer 1989 issue of Health Education Quarterly. These programs represent an important test of several tactical approaches to achieving healthy behaviors.

Child and Adolescent Trial of Cardiovascular Health (CATCH): This study is a collaborative health promotion field trial, which involves study sites in California, Louisiana, Minnesota, and Texas. The sites were selected for this school-based study to insure inclusion of public school students of different racial and ethnic backgrounds. The study will involve 96 schools and over 12,000 students. The findings should have widespread utility for all schools and groups. CATCH is using classroom curricula, changes in the environment such as school lunch and smoking policies, and family education to achieve the study goals. The three areas for intervention are dietary intake, physical activity, and cigarette smoking. The project includes a feasibility phase and a main trial. The main trial will randomize schools to one of two conditions: either control, or curriculum, school environment and a family component. The intervention strategies are based on behavioral research and have linkages across grades and across intervention components so that eating, exercise, and smoking changes are linked with curriculum, environment, and family. The intervention will take place in grades three through five. The follow up will take place in grades six and eight. The expected trial outcomes are changes in cholesterol and blood pressure plus decreases in sodium and fat content in the diet, decrease in smoking onset, and increase in physical activity and fitness levels.

Studies of Children's Activity and Nutrition (SCAN): This longitudinal study tracks food intake and physical activity patterns related to cardiovascular health in children who are three or four years of age at the time of entry into the study. Children from families with high risk for coronary heart disease or stroke will be compared with children from families with low risk for these diseases. Several risk factors in adults, including obesity and high blood pressure, are used for categorizing those at risk versus those not at risk. Five of the studies include an important component of black or Hispanic children, which will yield data more applicable to the general population.

NHLBI Growth and Health Study (NGHS): Obesity is regarded as a significant predictor of high blood pressures, diabetes, and coronary heart disease. It is a major public health problem for black women who have greater frequency of obesity, diabetes, and hypertension than white women. Obesity may have its origins in adolescence and may represent a major contributor to higher coronary heart disease mortality among black women. The NHLBI Growth Health Study (NGHS) will investigate the development of obesity in black and white female children and will assess the predictors of transition to the obese state, factors associated with this transition, and the relationship of this transition to other CHD risk factors. The results should provide a basis for effective therapeutic intervention programs for prevention of obesity. The study began in 1985 and included examination of parents or guardians of the children.

Dietary Intervention in Children with Elevated Low Density Lipoproteins (DISC): The primary objective of this study is to assess the feasibility, acceptability, efficacy, and safety of diet intervention in healthy prepubescent children, age 8-10 years at entry, who have elevated low density lipoprotein cholesterol (LDL-C) levels. School children are screened for high LDL-C levels, and those who are found are recruited for study. Participants are randomized to a usual care group, or to an intervention group.

The dietary intervention is based on the recommendations of the American Heart Association and the NIH Consensus Panel, and is intended to guide these high risk children toward maximum reduction in total fat, saturated fat and dietary cholesterol with compensatory increases in complex carbohydrate and water-soluble fiber. The eating pattern emphasizes fruits, vegetables, whole grains, low-fat dairy products and lean animal protein sources. Sodium reduction will be encouraged. In addition, participants will be advised to perform regular aerobic activity and to achieve ideal weight for height. Nutritional status will be carefully monitored through biochemical, anthropometric and dietary assessments. Normal growth and development and optimal intake of essential nutrients are the goals for the dietary intervention and control groups. Psychosocial development will also be evaluated and strategies for coping with peer pressure and other obstacles to optimal nutrition will be presented. Decreases in LDL-C levels will determine whether children will have a sufficient clinical response to reduce significantly their risk of atherosclerosis. Findings from this study will improve our understanding of the physiologic and behavioral effects of dietary intervention to lower elevated lipid levels in children that have high lipid levels.

These programs illustrate a concerted effort to promote healthy behaviors in children and adolescents and to identify successful cardiovascular disease prevention strategies early in life.

Mr. **Pursell**. In this case it was a cooperative effort. There was no follow through. When the study was over, the scientist was gone, and that is the end of it. That is the problem I have with a lot of scientific studies.

There is no applied part of HHS to pick up that piece of work that was well-done, well-financed, we are paid for it and I support it. But, it just lays there like a lot of other grants.

So, we take the first part and we do the basic research, but that is it. We stop there and we don't carry through.

It seems to me there ought to be some kind of a linkage somewhere within the whole department, not just you, but beyond the NIH that says, "All right, we have got a good, marketable study here that we can put into the school system and get it out, a further partnership and coordination effort that you spoke about."

I really don't see that happening at all.

Dr. **Lenfant**. I can assure you, and I will make it a point of providing data on this, that there is an awful lot of research outcomes being disseminated to the public.

Our Institute alone has a number of educational programs on cholesterol, and other cardiovascular risk factors.

In many of these programs the school environment is a target. In fact, a couple of weeks ago, we did release a report which discusses control of blood cholesterol and better dietary habits. Our recommendations are for the whole population including school age.

Mr. **Pursell**. In the elementary system, some of the statistics I am reading from your various departments, obesity is a large, serious issue in early grades which translates into heart disease, right really into your Institute, the problem on your turf.

Dr. **Lenfant**. Absolutely.

You may not know, Mr. Pursell, but the department has developed what it calls the "Year 2000 Objectives." Some of these objectives are to do what you are talking about.

It is being done in our Institute and I am sure the other Institutes as well. We are working with the Centers for Disease Controls. We have a very good cooperation to reach the community level.

I have to admit that you have a point, often the research outcomes are not utilized as fully as they could be.

Mr. **Pursell**. Thank you, Mr. Chairman.

Mr. **Natcher**. Mr. Early?

CARDIAC ENERGETICS

Mr. **Early**. Thank you very much, Mr. Chairman.

Dr. Lenfant, it is always a pleasure to see you. I couldn't agree with Mr. Pursell more. That study went where all the other studies went. We study it, spend our money and never apply the study. Mr. Stokes spoke of the Framingham Study.

That study has been ongoing for over 40 years. Mr. Stokes spoke about what is happening, what it reveals, and we don't do anything with regard to what it tells us about the black and elderly populations except talk about it.

Last year, Funds were provided for the establishment of a new laboratory of cardiac energetics. What is the status of that project? Isn't that the money for the magnetic resonance imager?

Dr. LENFANT. Yes.

Mr. EARLY. What is the status of that project?

Dr. LENFANT. It is almost done. I am very embarrassed to say almost done. Yesterday and today, I believe, there was lots of talk about bureaucracy and government process. Here is a case in point for you.

It really took a long time to get all the bidding done to procure the equipment. The bottom line is the contract has been let, the equipment has been purchased and it is being assembled now. We need space to put that machine at NIH.

The ground is going to be broken next month. The new laboratory is going to be completed and open up in November of this year. I would like to extend and invitation to you to come and see it.

Mr. EARLY. Don't put the date on the invitation for a while.

Dr. LENFANT. This time I can.

Mr. EARLY. Is that a GE?

Dr. LENFANT. Yes.

Mr. EARLY. The private sector would have taken one month to get that.

Dr. LENFANT. Mr. Early, I, working for the government, cannot go buy a piece of equipment that cost $3.5 million in one month.

Mr. EARLY. I am not sure we are working for the government anymore and not just hanging around with the government.

How much is in your 1991 request for that laboratory, Doctor?

Dr. LENFANT. I will provide for the record the exact amount. It is probably on the order of $3 million.

[The information follows:]

LABORATORY OF CARDIAC ENERGETICS

The 1991 budget for the Laboratory of Cardiac Energetics is currently estimated at $3,141,000.

PRIORITY AREAS FOR ADDITIONAL FUNDS

Mr. EARLY. I want to know if any additional funds are needed for 1991, and if so are they in your budget request?

Under the request the Heart, Lung, and Blood Institute will fund fund 718 new grants. While it is somewhat of an increase over the 1989 level, it is below the level of new and competing grants that Heart, Lung, and Blood Institute has funded in the past.

What new opportunities could we support if additional funds for research were available?

Dr. LENFANT. There are many research opportunities which are in all of the programs of the Institute, that is in heart, lung, and blood disease. I could give you specifics.

Mr. EARLY. Would you provide that for the record, and go into some detail on that?

Dr. LENFANT. Indeed.

[The information follows:]

RESEARCH OPPORTUNITIES WITH ADDITIONAL FUNDS

Although the Institute can maintain research progress with the President's Budget funding level, there are numerous scientific opportunities that could be pursued if additional funds were available. High priority opportunities exist in each of the major program areas of the Institute. They are described in the following material.

Specialized Centers of Research (SCORs): Given additional funds, the Institute's first priority would be the restoration of reductions to its existing SCOR programs. These research centers provide a unique opportunity for basic and clinical scientists from a variety of disciplines to collaborate on research in a particular disease area. It should be remembered that the NHLBI is an Institute with a focus on specific clinical conditions, and a large measure of its success comes from the rapid translation of research findings to the bedside. The SCOR program is critical to that effort because it is uniquely and often exclusively the Institute's avenue for clinical research in a given disease area. The program ensures that advances in basic sciences are translated rapidly into clinical application and that clinical needs provide direction for the basic sciences. Over the years, work performed in the Institute's SCORs has contributed directly to the betterment of public health through improvements in the prevention, diagnosis, and treatment of disease. Recent research has produced enormous gains in our understanding of fundamental disease mechanisms that can rapidly be translated into new therapeutic interventions. The SCOR program is the NHLBI's best instrument for achieving that evolution.

The NHLBI has identified three new areas of scientific need for expansion of the SCOR program: Vascular Biology and Medicine, Sudden Cardiac Death, and Heart Failure. The FY 1991 cost of these new SCORs is estimated at $20 million.

Vascular disease, which cuts across the NHLBI programs in heart, lung, and blood disease, is important from the standpoint of its high incidence, serious morbidity, and significant mortality. Presently, no one clinical discipline is focused exclusively upon the diseases of the vasculature and, consequently, lessons learned by researchers in one of the related disciplines may be shared only within that discipline. New developments in the basic sciences, particularly in the fields of cell biology, molecular biology, and biochemistry, are bringing to light much knowledge about how cell behavior and communication affect the vasculature in health and disease. The SCOR in Vascular Biology and Medicine will provide an integrative environment for research to improve understanding of vascular disease and to develop and refine methods for its detection, management, and prevention.

Sudden cardiac death claims over 270,000 Americans annually and accounts for about 50 percent of all deaths from coronary artery disease. Yet, the mechanisms triggering the lethal arrhythmia remain obscure. Basic knowledge about electrical activity in cardiac tissue has been developed, but has yet to provide leads directly applicable to the clinical event. The Institute believes that the multidisciplinary, collaborative atmosphere of a new SCOR program will provide the impetus to translate basic electrophysiologic studies into clinically useful diagnostic and therapeutic approaches as well as foster the pursuit of new knowledge. Recent reports of an association between circadian rhythm and sudden cardiac death similar to that demonstrated for myocardial infarction provide clues to the pathophysiologic events precipitating a lethal arrhythmia. The new SCOR in Sudden Cardiac Death would pursue these research avenues.

The new SCOR in Heart Failure will address a condition that currently affects about 2.3 to 3.8 million Americans and is becoming an increasing problem as the population ages. For most patients with heart failure, therapy is palliative; the only treatment available for end-stage heart failure is a heart transplant. The NHLBI continues to pursue vigorously a number of therapeutic strategies, such as treatment with vasodilator drugs and the development of the artificial heart. Nonetheless, it is apparent that success in the clinical area depends on the existence of a parallel effort in basic research. At present, very little is known about the underlying mechanisms of heart failure. The relative roles of changes in gene expression, receptor regulation, ion channel and pump maintenance, and metabolic activity in myocardial dysfunction are poorly understood. Further, there are many unanswered questions about the mechanisms whereby cardiac myocyte necrosis occurs as a result of changes in structure and function of the heart and the coronary circulation. New knowledge of the pathophysiology, biochemistry, and molecular biology of heart failure will lead to improved strategies for the clinical care of patients with this condition.

National Marrow Donor Program (NMDP): The Institute has developed plans to expand the NMDP so that it may better meet the needs of the American people. The registry now lists nearly 100,000 potential donors, which had been the original goal, but it is now apparent that at least 250,000 donors are needed to provide a reasonable chance of matching any given patient with a donor. Further, there is a pressing need to include many more minority and international donors. Reaching the new goal of 250,000 will require that an additional 150,000 persons be typed for HLA A and B antigens, at an estimated cost of $12 million to $14 million. Performing HLA-DR testing as well could be expected to double these costs.

The NHLBI also plans to expand its National Blood Resource Education Program to include public and professional education about bone marrow transplantation. Considerable media attention has been given to the plight of individual patients for whom donors are difficult to find, and a number of patient-focused, crisis donor recruitment drives have been undertaken. Measures need to be taken to ensure that prospective donors provide informed consent and meet certain requisite health criteria, and that samples are collected properly and efficiently. Given the prospects for expanded interest in bone marrow donation, an educational effort is essential to address these needs. The Institute estimates that $1 million is needed for this purpose.

Bone Marrow Transplantation and Gene Therapy: The NHLBI is planning a major expansion of its intramural gene therapy research program that is concordant with, and dependent upon, the parallel development of a clinical bone marrow transplantation (BMT) unit at the NIH Clinical Center. The estimated cost of the total program is $5 million in FY 1991.

The NHLBI intramural research program is engaged in a important effort to develop effective methods of genetic therapy for heritable human diseases within the Institute's mandate. Having successfully completed the world's first gene transfer experiment in humans, the program is embarking on new gene therapy protocols of historical significance. Currently under review is a protocol to treat adenosine deaminase (ADA) deficiency, a genetic disease that causes severe combined immune deficiency. This research is expected to have applicability not only to other bone marrow and genetic disorders, but also to revolutionary new treatments for cancer, viral disease, and cardiovascular disease. For example, the transfer and expression of the newly identified gene for cystic fibrosis in bronchial epithelial cells is being investigated. Use of gene therapy to treat such hemoglobin disorders as sickle cell anemia and severe Cooley's anemia is also under study. Gene therapy might also be used to alter cholesterol metabolism, thereby reducing the risk of heart disease in a wide patient population.

The possibility of treating genetic diseases through modifying the genome of somatic cells by gene insertion seems likely to be achieved in the next several years. It is probable that such experimental treatment will occur initially in the context of bone marrow transplantation (BMT). Accordingly, the NHLBI is planning to lead an intra-NIH effort to establish a clinical BMT unit in the NIH Clinical Center. The availability of a dedicated facility for BMT would enable intramural scientists to extend findings from their basic research laboratories and attempt innovative, experimental, therapeutic interventions for specific diseases. The BMT unit is needed to conduct investigations relative to the refinement and use of BMT therapy; more important, it is a critical resource that is needed to fully develop the overall gene therapy program. The presence of such a facility would assure the ability intramural scientists to assume a leading role in the development of this most promising area of research.

Before gene transfer can be considered as a therapeutic option in humans, substantial investigation will have to be performed in non-human primates to evaluate the efficacy and safety of gene transfer protocols. Various parameters that influence gene transfer into the hematopoietic stem cells of primates have been explored within the context of the Institute's existing primate bone marrow transplantation-gene transfer program. Although the results of the stem cell work are extremely encouraging, much additional work is required to increase the efficiency of gene transfer to a level that will be consonant with therapeutic applications. Consequently, the NHLBI is planning a major expansion of its primate gene transfer program.

The planned expansion will complement significant extramural research program designed and implemented by the Institute. For example, the NHLBI is supporting research to identify the location, function, and mode of action of genes that play a significant role in the pathogenesis of hypertension and to develop and use transgenic animals to study hypertension. If the genes contributing to the pathogenesis of hypertension can be identified and animal models of the disease process can be created, new therapeutic approaches may be developed.

Coronary Heart Disease (CHD) Prevention: Hypertension, which affects about 58 million Americans, is a major risk factor for the most commonly encountered forms of heart and blood vessel diseases. It accelerates the development of atherosclerosis of the coronary and peripheral arteries and is the single most important contributing factor to the development of stroke. During the past 20 years, many improvements have occurred in the control of hypertension. The public is more knowledgeable about hypertension, more likely to visit a physician for hypertension, and more likely to follow medical advice. During this same period, there has been a 57 percent decline in the national age-adjusted stroke mortality rate.

The overall health benefits associated with treating hypertension have been well documented. However, studies to determine whether treating mild-to-moderate hypertension reduces heart attacks and deaths from coronary heart disease have produced equivocal results, possibly because of the confounding influence of adverse effects of the drugs used in such studies. New classes of drugs have been increasingly recognized as possible approaches for initial treatment of mild hypertension, but there has not been a conclusive study of their comparative effectiveness. A recent report in the hypertension literature noted that "...large scale trials have not used newer antihypertensives such as calcium antagonists and angiotensin converting enzyme inhibitors. There are no comparable data for these widely used drugs, and we urgently need large scale comparative trials to assess the role of these agents as first line treatments in mild hypertension."

The NHLBI proposes to initiate a clinical trial to compare new antihypertensive medications with current therapy to determine whether the newer approaches are capable of achieving a reduction in the number of nonfatal heart attacks and the mortality from coronary heart disease. The total duration of the trial, including planning, intervention, follow-up of 7-9 years per patient, and data analysis, will be 12 years. Estimated first-year costs are \$2.6 million; estimated total costs are \$143 million.

Mechanisms of Bronchopulmonary Dysplasia: Bronchopulmonary dysplasia (BPD) is a chronic lung disease of infancy that affects about 8,000 babies born in the United States each year. Although mainly a consequence of neonatal respiratory distress syndrome (RDS), a complication of prematurity, BPD has also been reported in infants with pneumonia, meconium aspiration, cyanotic congenital heart disease, and apnea. The incidence of sudden infant death syndrome (SIDS) is about seven times higher in infants with BPD than in normal infants.

The NHLBI proposes to expand and diversify its program of basic research on BPD. The recent development of new cellular and subcellular approaches for investigation of pathogenetic mechanisms has created opportunities for morphologic, physiologic, cellular and molecular level studies of BPD. Detailed studies are needed of pulmonary function as it relates to lung morphology and biochemistry during lung injury, recovery, and growth in subjects at various stages of disease. A need also exists to develop cytological, biochemical, and molecular information on cellular events associated with lung development and with lung injury in premature newborns during the first few weeks of postnatal life.

The Institute will also encourage studies of neuroendocrine cell function, growth factor expression, receptors, and collagen production, including that of basement membranes and their role in the repair process under both normal circumstances and conditions of widespread scarring. Studies directed at understanding protease/antiprotease balance, inflammatory mediators, and cells of the immune response are also needed, as well as research to identify the cell populations involved in the regeneration of badly damaged lungs. This research will shed light on the natural history of BPD and on the pathophysiology of BPD in comparison with normal lung development. The findings will add considerably to our knowledge of how to prevent and treat BPD, and may be expected to lead to a greater understanding of lung injury and repair in other conditions as well. The estimated cost of this expanded program is $2 million in FY 1991.

Prevention and Treatment of Asthma in Children: Asthma is a serious chronic disease affecting approximately 10 million people in the United States, 3 million of whom are under the age of 18. Costs from asthma care exceed $4 billion per year. Asthma is probably the only treatable condition whose prevalence and severity is increasing, attesting to the need at the national level for asthma education and more effective treatment of this disease.

Since the mid-1970s, behavioral research has addressed ways of teaching asthmatics and their families to manage the disease. Asthma education programs have resulted in fewer attacks, better adherence to medication, fewer days lost from school, fewer visits to the emergency room, and improved school grades. These findings have been disseminated widely. The National Asthma Education Program (NAEP), initiated by the NHLBI in 1989, is expanding these efforts.

Because of recent evidence suggesting that childhood asthma predisposes one to subsequent development of chronic obstructive pulmonary disease (COPD), and that the course of COPD is most severe in patients with low initial lung function levels, the NHLBI proposes to initiate a clinical trial to examine the effects of a structured, stepped-care drug intervention program in maximizing and maintaining optimal lung function in children and reducing the risk of lung disease in later life. If our hypothesis proves correct, this program should greatly benefit children who would otherwise grow up with an increased risk of lung disease, and the high medical costs and suffering that go with it. The estimated first year cost of this clinical trial is $1 million, and total costs are $40 million over nine years.

National Heart Attack Alert Program: Coronary heart disease (CHD), the leading cause of death in the United States in both men and women, caused 511,000 deaths in 1988. People with CHD often do not reach appropriate medical care, and those who do often do not reach it in time for the latest life-saving technologies to be effective. Minimizing the damage resulting from a heart attack by preserving cardiac tissue is of paramount importance.

The Institute has been considering the establishment of a national education program to alert health professionals, their patients, and the public about the need to respond with immediate action at the first signs or symptoms of a heart attack. Recent scientific advances and especially the development of thrombolytic therapies have provided effective methods for reducing the morbidity and mortality associated with CHD. Yet available data suggest that only a small percent of the heart attack patients eligible for thrombolytic therapy actually receive it.

In September 1989, the Institute convened a small workshop of leading experts in cardiology, emergency medicine, and behavioral medicine to assess the advisability and feasibility of creating an education program to emphasize the need for early heart attack intervention. The NHLBI was advised to proceed with due caution in developing the program. The workshop recommendations were sufficiently thought-provoking to prompt the Institute to consider the issues in more detail.

The Institute will sponsor a forum entitled "Rapid Identification and Treatment of Acute Myocardial Infarction: Issues and Answers" in October 1990. Key issues will be introduced by recognized experts and discussed by forum participants who will then formulate their recommendations. Proceedings of the forum will be prepared and disseminated throughout the scientific community to increase awareness of the issues and to secure a broad range of comments concerning the proposed educational effort. The proceedings will also be used by Institute staff to weigh the advisability of establishing a program and to determine how such a program should be structured.

Mr. **Early**. What would the downward negotiation for competing and noncompeting grants be for your Institute?

Dr. **Lenfant**. The downward negotiation for next year in the competing, we estimate that it will be in the order of 14 percent and for the noncompeting——

Mr. **Early**. On the competing, is that for this year?

Dr. **Lenfant**. For this year it is more than that.

Mr. **Early**. For 1988, it as 14.9 percent?

Dr. **Lenfant**. No. For 1988, the reduction was—excuse me. You were correct. It was 15.3.

Mr. **Early**. 15.3, 11.5 for 1989, and 13.9 for 1990?

Dr. **Lenfant**. Excuse me for interrupting, Mr. Early. The fact of the matter is that this year the reduction is much higher than that for competing grants.

Mr. **Early**. Doctor, as I understand, for noncompeting, it is 8.6 for 1988; 13.3 for 1989, 14.5 for 1990 and 11 percent under this request. Will you provide the accurate figures for the record? Isn't this devastating to research?

Dr. **Lenfant**. It is. We have a problem.

Mr. **Early**. Is there any good scientific reason for doing this?

Dr. **Lenfant**. No scientific reason.

[The information follows:]

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

RESEARCH PROJECT GRANTS

PERCENTAGE DOWNWARD NEGOTIATIONS

Fiscal year	Noncompeting projects	Competing projects
1985	−0.3	−1.5
1986	−4.7	−7.8
1987	−1.1	−10.9
1988	−9.6	−14.9
1989	−13.3	−11.5
1990 estimate	−14.5	[1] −13.9
1991 estimate	−11.0	−13.9

[1] The 1990 estimate of the reductions necessary in competing research project grants is calculated using the NIH total competing requirements model. The calculation is done before the fiscal year begins. As a result, different reductions may be necessary once applications to be funded are actually received and reviewed.

RESEARCH CENTERS

Mr. **Early**. The budget justification says you plan to fund 64 research centers in 1990 and in 1991. Your 1991 request shows level funding for the centers program.

The funding level is less than that in 1989. I assume research centers will be subject to downward negotiations?

Dr. **Lenfant**. Yes, sir.

Mr. **Early**. What will the percent be?

Dr. **Lenfant**. Approximately 18 percent.

Mr. **Early**. That applies to both competing and noncompeting centers?

Dr. **Lenfant**. Yes, sir.

Mr. Early. Doctor, you have been here several years. What happened when you told us that 10 percent would be devastating? Did you fib to us or did you make an error?

Was it devastating?

Dr. Lenfant. I think my first thought was in error. I could not anticipate that the reductions would grow as fast as they have.

Mr. Early. Do you think the downward negotiations really cause us some loss?

Dr. Lenfant. I think it is a problem. As you know, Mr. Early, as I have mentioned to you each year, our center program supports most of the clinical research in our Institute. We have a problem today.

Mr. Early. What effect will this have on the centers and their research programs in your professional opinion?

Dr. Lenfant. A very significant one. It is difficult to answer with precision. If you may recall, the one chart that looks like a tree. You see all these steps. Each represented a scientific outcome and about nine out of ten of these outcomes which were on this chart came from our research centers.

Mr. Early. That chart also showed the time of stay in the hospital was going from 10.6 to 6.9. What if you don't have these centers? What if there are downward negotiations? Is that going to be accurate.

Dr. Lenfant. What you saw is the result of significant research. If there is less research, I guess we will see less outcome. I wish I could be more precise than that, but I can't.

Mr. Early. That is what Mr. Pursell is talking about. We just studied to study. We don't apply it. Now we are going to have downward negotiation that might put that off track. How important is the centers program to the National Heart, Lung and Blood Institute Research program, in your opinion?

Dr. Lenfant. I would say it is an important part of our clinical research program.

PEDIATRIC AIDS

Mr. Early. Doctor, in fact, there has not been an increase for the centers program since 1987, has there?

Doctor, the pediatric AIDS people are looking to NCI and your institute. Bring us up to date on what your Institute is doing in the area of pediatric AIDS?

Dr. Lenfant. We have a program in pediatric AIDS. We see more and more newborns and infants with AIDS, having been contaminated by their mother. One of the biggest issues about these kids, is how their disease is going to evolve. As you know we are extending the lives of patients with AIDS more and more, even young children. The problem is that they develop a number of complications, particularly pulmonary and cardiac complications. In our pediatric AIDS program we look at the extent and magnitude of these complications, that is look at the natural history of those complications and assess what is the best way to treat these infants and newborns.

Mr. Early. In the area of treatment, we should study these things and apply them.

Chairman Natcher does not like to earmark, nor do I, but when we talk about pediatric AIDS, would that encourage a collaborative type of effort among NCI, your Institute and perhaps the child health program?

Would that be earmarked?

Dr. LENFANT. No. In fact, our project is—we work together, and they bring their resources and their experiences and we bring ours.

Mr. CONTE. Right.

Would a pediatric AIDS center, a comprehensive center, with clinical trials and applied research would that be the way the pediatric AIDS applicants probably should go?

Dr. LENFANT. That is basically what is being done.

You see, there are, I think, there are approximately 2,000 young infants with AIDS. Therefore, they cannot be divided among all the Institutes.

What is happening is that all the Institutes work together on this population, each bringing its own expertise and qualifications.

The Allergy and Infectious Disease Institute is working on the pathogenesis of the condition. Dr. Broder as you heard this morning is looking at how you can prevent the occurrence of the transmission of the disease in infants.

And we are looking at these infants who are having the disease but on whom we need to study pulmonary and cardiac complications, which is basically from what they die.

Mr. EARLY. If Mr. Natcher and Mr. Conte decide to support a pediatric AIDS center, I don't think we are doing anyone a service if we start one and then we start downward negotiations of all the other centers to find the money.

I have heard you say to the Chairman that we are on the borderline with downward negotiations that are so extreme. I would guess that you would say that we should reduce the number of centers and maintain the necessary tools in the centers that we keep open.

And I agree. I think it's bureaucracy that we are funding when we keep downward negotiating and don't give the centers the tools to do the job.

Thank you.

Mr. NATCHER. Mr. Dwyer, I yield to you.

FDA AND FOOD LABELING

Mr. DWYER. Thank you, Mr. Chairman.

I came in very late, and I don't want to be redundant in asking a question, but I don't think anyone has mentioned the Drug and Food Administration's intention to improve the labeling of food products to include the food's actual cholesterol content.

Have you worked closely with the Food and Drug Administration on that labeling, Doctor?

Dr. LENFANT. We have been consulted by the Food and Drug Administration, and we do agree with what they are doing. We think they are doing the right thing, and that food labeling is going to be of great help to the American public, provided that it's complete food labeling.

You see, what we have seen during the last few years is something which, in my opinion, has distorted the whole picture.

You have seen some food manufacturers saying well, my food has no cholesterol. That may be true that there is no cholesterol; and for that matter, there may never have been any cholesterol in it. But they don't say anything about saturated fat, which is the important component.

What is happening now is that the Food and Drug Administration is going to require a labeling addressing all the components of these food products; and that, I think, is going to be very useful to the American people.

Mr. DWYER. Well, I guess the question I really want to ask, are they taking your Institute's advice on what that labeling should actually consist of?

Dr. LENFANT. Well, sir, I would not say that I—I wouldn't call it necessarily advice, but certainly they talk to us. We work with them. I have members of my staff who are in daily communication with the Food and Drug Administration.

We serve on their committee. They serve on our committees. So it's clearly good communications, and they know what we stand for. Yes, they do ask our advice.

Mr. DWYER. Did they ask your help in fighting the food industry?

Dr. LENFANT. No, no, and we, of course, couldn't do that.

Mr. DWYER. Okay, Doctor.

I am going to have some questions for the record, Mr. Chairman. I am sorry I was late today.

Mr. NATCHER. That is all right.

Mr. Porter.

ARTIFICIAL HEART PROGRAM

Mr. PORTER. Thank you, Mr. Chairman.

Dr. Lenfant, I want to talk about the artificial heart program. Surprised?

Dr. LENFANT. No.

Mr. PORTER. You really have two tracks going. One is you're developing an artificial heart that is a true artificial heart, but it's not fully implantable. That is, it has to be partly outside the body.

And then you have the long-term assist device called the left ventricular assist device that is fully implantable; correct?

Dr. LENFANT. Well, excuse me, Mr. Porter. The total artificial heart is a device that would be fully implantable.

Mr. PORTER. Okay.

Can you tell us about the program, how many contractors you have and what they are doing. What about clinical trials?

Dr. LENFANT. Yes. Just for the sake of history, you do recall that a couple of years ago there was some discussion as to whether we would do the two tracks at the same time. Congress expressed its wish that the two avenues be pursued at the same time; and that is what we are doing.

Let me first talk about the total artificial heart program, which is to replace the natural heart by the device. In January we began the third year of a five-year program. So we have almost three years to go.

There are four teams working and the work is going well. There are a number of questions that need to be addressed and while the work is going on, they have asked the Institute of Medicine of the National Academy of Sciences to do an extensive review of the total artificial heart program.

We expect to have the report from the Institute of Medicine early next year in time for us to make a decision as to what we are going to do at the end of this five-year period.

I cannot anticipate what the Institute of Medicine will say, but I think that there are reasons to believe that we will be presented with good arguments to continue the program. But we will see.

Mr. PORTER. Wouldn't this type of artificial heart have to have a power source that is external to the body?

Dr. LENFANT. There will be an internal power source that will be recharged through the skin.

Mr. PORTER. Through the skin.

Dr. LENFANT. Through the skin by induction. You will have the artificial heart in the chest, and then there will be a battery system which will be in the abdomen. Around the abdomen, you will have a belt with a system that will transfer the energy through the skin into the battery, which is inside the abdomen.

And, in fact, the expectation is that the outside source of energy, be replenished by plugging it into your cigarette lighter on your automobile or something of that sort.

So that is the total artificial heart program. I have to tell you in all honesty, I think we are well away from having that implanted and having people move about with an artificial heart.

Mr. PORTER. Well away?

Dr. LENFANT. Oh, yes. I would say 10 years, in my opinion.

Now, the left ventricular system is not a replacement system. It's a support system. In other words, you would leave the natural heart in the chest, but it would be a failing heart and you would support it. You would assist it with that device.

Here, you have this device in the abdomen, going from the device to the natural heart. There will also be an outside source of energy.

Now, this program is much, much closer to human applications. We have completed reliability tests in the sense that we have had some of these devices which have been functioning without interruption for more than two years on the laboratory bench.

And so we feel pretty confident that if they have gone two years, they could probably go another two years or more.

These devices are being built now, and we have issued a request for proposal for universities and hospitals to submit applications to become clinical centers to do a clinical trial to assess the efficacy of these devices.

Our expectation is that these devices should function without interruption or problems for a minimum of two years. But this is a very rigorous assessment, and in fact we expect that they will all function for probably five years.

Mr. PORTER. How far are we away from the LVAD device? How long will the clinical trials last?

Dr. LENFANT. I would say probably two to three years.

Mr. PORTER. Two to three years.

Dr. LENFANT. Yes, sir.

Mr. PORTER. To complete the clinical trials?

Dr. LENFANT. The clinical trials should begin sometime this year.

Mr. PORTER. That is fine. I am glad to hear it. In fact, I appreciate your leadership on the whole artificial heart program. I think you are making real progress.

Dr. LENFANT. Thank you.

CORONARY BYPASS SURGERY AND ANGIOPLASTY

Mr. PORTER. We have seen some—and perhaps you discussed this when I wasn't here, but there have been reports in the press that the coronary bypass procedures in many cases are unnecessary, that a lot of unnecessary surgery has been performed.

Do you agree with that, and what should be done?

Dr. LENFANT. Well, I don't know that I am truly in a position to say whether this assessment is true or not. What I know is that today, although the number of coronary bypass cases done each year keeps on increasing, it's largely because many patients who have had it for the first time years ago are now coming back for a redo. So the bottom line is I think that the number of new cases is leveling out.

Now, whether this number—number of first cases, whether this number is in excess of what is truly needed, I am really not in a position to say.

All I can say is that we have an ongoing study which is comparing the efficacy of coronary bypass surgery with what is called angioplasty. You know, it's putting a balloon into a coronary artery and inflating it to dilate the artery so that the blood will flow through.

This study should be completed in a couple of years. If it would show and I have no idea of what the outcome is going to be, that angioplasty is as effective as coronary bypass surgery I think it would lead to a reduction in the number of coronary bypass cases each year.

From the viewpoint of cost we are talking big money. Coronary bypass surgery is $30,000 to $35,000. Angioplasty is in the $5,000 bracket, so it's a substantial difference.

Mr. PORTER. And that would be the major alternative to having coronary bypass surgery, angioplasty?

Dr. LENFANT. Yes, sir.

Mr. PORTER. Thank you very much.

Mr. NATCHER. Off the record.

[Discussion off the record.]

CHOLESTEROL EDUCATION PROGRAM

Mr. NATCHER. Doctor, one of your newer public education activities relates to cholesterol, as you know. Last fall, a widely read article in a national magazine challenged the basic premise of this program.

Let me just read you a short quote, "Lowering cholesterol is next to impossible with diet and often dangerous with drugs. It won't make you live any longer."

And Doctor, I am sure that you have seen this one. I show you here the front cover of the Atlantic Magazine.

On top of this, the Inspector General has testified that most testing programs are grossly inadequate. What do you do about criticisms like this, Doctor? Do you just ignore them, or do you think about them? What do you do about it? What would you say on the record?

Dr. LENFANT. Indeed I know about this article. And it has been, to put it mildly, a bit of a headache for a few weeks after its publication, but there it is.

We believe very strongly that the premises of the article were just off base. The gentleman who wrote this article presented one side of the issue, What he said, I think, has not been true nor helpful to people in need of doing something about their cholesterol.

There are numerous studies from this country and other countries which have demonstrated that you can lower cholesterol and that if you do so, you decrease the risk of coronary heart disease.

And, in fact, some very recent studies have further shown that if you have coronary arteries which are partly obstructed by cholesterol deposits, if you reduce the blood cholesterol then this—there will be a regression of the obstruction in the coronary artery.

So we really believe that is what was said in this article was not appropriate. The fact remains that we take these criticisms very seriously. We look at them in a positive way in the sense that what it seems to be telling us, "you didn't do a good job, you didn't send your message out there as well as you could have done it."

And so we are addressing these issues now, and although we are very confident that the basis, the scientific basis of what we recommend is very strong, we do recognize that there are a number of issues and questions which still need to be answered. We are working very hard to answer these questions.

So the publication of this article was a regrettable event. It's behind us now, but I am sure that unfortunately, some other criticism will be raised, but the bottom line is that the American people are by and large responding positively to our recommendations.

Now, the second issue that you raised is the report from the Inspector General. Well, this report was well founded; what he had to say was quite appropriate. It's most distasteful that in the country there are indeed a number of public cholesterol screenings which are performed by amateurs who don't know what they are doing.

I could paraphrase what Dr. Broder had said this morning, the result of a procedure or measurement is never going to be any better than the person who does the work. Basically this is what he said. It's true for mammography; it's true for cholesterol measurement.

However, we were very well aware of poor measurements, and we have convened a task force to develop guidelines on how to perform the best possible public cholesterol screening.

Certainly, Mr. Chairman, you know that at the end of his report, the Inspector General said that organizers of public cholesterol screening should follow the guidelines of the Heart, Lung, and Blood Institute. This made us very happy, and now we are working hard to widely distribute and continue to improve the guidelines.

Mr. NATCHER. Doctor, when you get the transcript back, can you tell us how much money is budgeted for the cholesterol education program in 1990, 1991, make a rightful statement in here.

Doctor, we will be questioned about this, and we would like your answer, Doctor.

CHOLESTEROL EDUCATION PROGRAM

The Institute looks at the total amount available for all its education programs rather than focusing on a budget for the individual education programs. At present, the Institute divides the amount available for education programs into two funding pools. One pool of funding is allocated so that a specific sum of money is identified with each of our several education programs. The second pool of funds supports several or all of the education programs. Included in this pool are crossover initiatives such as multiple risk factor education efforts, initiatives implemented at the worksite, and initiatives that target special populations such as those directed toward a specific minority group. Staff salaries and related support costs are also included in this second pool. It is not possible to attribute accurately the costs in this pool to a specific education program.

Costs that are specifically identifiable with the National Cholesterol Education Program are $1,435,000 in FY 1990 and $1,362,000 in FY 1991. The overall budget for the Institute's education activities, including the National Cholesterol Education Program, National High Blood Pressure Education Program, NHLBI Smoking Education Program, National Asthma Education Program, National Blood Resources Education Program, and National Heart Attack Alert Program is $5,736,000 in FY 1990 and $6,056,000 in FY 1991.

This concludes the hearing on this Institute for the fiscal year 1991.

Dr. Lenfant, as you well know, it's always a pleasure to have you appear before our committee. This has been a good hearing, Doctor, and we appreciate it.

Mr. CONTE. Mr. Chairman, I have many questions to ask you, but I will submit them for the record, and you can answer them.

Dr. LENFANT. Please do. I will do my best to answer them.

Mr. CONTE. I get the message here loud and clear.

Dr. LENFANT. Thank you very much.

[Questions and answers for the record and the justification follow:]

QUESTIONS SUBMITTED BY THE SUBCOMMITTEE

RESEARCH TRAINING

Mr. Natcher. The report which you issued, as well as the recent National Academy review were particularly disturbing in their findings about physician training. Your report says that less than half of these individuals ever even submit an application. The Academy says the figure is less than 10 percent. What can you tell us about these numbers.

Dr. Lenfant. While the NIH believes that improvements are necessary in its biomedical research training programs for physicians, it is certain that the programs are performing better than the Academy figure suggests. Data included in the Task Force report on the "Review of the National Institutes of Health Biomedical Research Training Programs" show that nearly 45 percent of those individuals who trained longer than 24 months while 27 percent of those who trained 12 months or less applied for NIH research or career development grants.

The disparity between the data presented in our Task Force report and the Academy report may be due to several differences: 1) the NIH support mechanisms included in our report were all research grants and career development grants while the Academy report included only regular research grants; 2) the cohort of trainees in our report included those trained between the years 1976 and 1982 while the Academy report included only trainees who began training in 1982; and 3) our follow-up data is for applicants from 1976 to 1986 while in the Academy report follow-up was from 1982 to 1987. Whatever the source of the difference, we are committed to making changes in our biomedical research training programs that will increase the percentage of physician trainees who apply for and receive NIH research support. As you know, a detailed plan is being developed to implement the recommendations of the Task Force report.

Mr. Natcher. The Academy report states and I quote, "Only 8.5% of M.D. trainees who began NRSA training in 1982 applied for R01 grants." Is this accurate?

Dr. Lenfant. The 8.5 percent figure reported in the Academy report reflects only those individuals who began training in 1982 and who, by 1987, had applied for an R01 grant. Our Task Force examined the applications submitted for all of the available mechanisms of support through 1986 by all individuals trained between 1976 and 1982 and found that 32 percent had applied.

The fundamental goal of our biomedical research training programs is to prepare well-trained, highly qualified, and productive research investigators. We have several mechanisms of support available for new investigators, only one of which is the regular research grant (R01). Many choose to apply first for a career development grant (K-series) to develop independent research skills and experience. Others may choose to apply for the First Independent Research Support and Transition (FIRST) grant which provides an initial period of research support to allow new investigators to demonstrate the merit of their research ideas. Finally, those individuals who have reached a more independent level of development may elect to apply for a regular research grant (R01) to support a specific research project in their area of interest.

Mr. Natcher. The Academy is recommending that these M.D. programs be put on hold until the current system can be evaluated and corrective action taken. Will NIH follow this recommendation?

Dr. Lenfant. In April 1989, I was asked by Dr. Wyngaarden, the then Director of the NIH, to chair an NIH Task Force to review the programs and make recommendations to strengthen them. The result of our efforts is detailed in the report entitled, "Review of the National Institutes of Health Biomedical Research Training Programs." Included in the report were a number of recommendations that, when fully implemented, should significantly improve the effectiveness of the programs in developing new biomedical investigators. As I said earlier, the NIH is now developing a plan to implement the recommendations of our Task Force and I am sure that, in doing so, the NIH will also look at the recommendations of the Academy.

NATIONAL MARROW DONOR PROGRAM

Mr. Natcher. Would you review for the Committee briefly your 1989, 1990, and 1991 spending plans for the bone marrow registry?

Dr. Lenfant. For FY 1989, Congress made available $4.0 million for the National Marrow Donor Program (NMDP) of which $1.5 million to NHLBI and $2.5 million to the U.S. Navy, later transferred to the NHLBI. Of this, $328,654 was used to fund two relatively small contracts for marrow donor recruitment and related research. One of these is to the Puget Sound Blood Center in Seattle; the other, to the Blood Center of Southeastern Wisconsin in Milwaukee. The NMDP contract to the American Red Cross had $3,671,346 available. For FY 1990, the Institute will provide $3.6 million for the NMDP. Currently, the NHLBI is planning for $3.9 million to be devoted to the NMDP during FY 1991.

Mr. Natcher. Several recent cases have generated interest in federal funding to expand the size of the registry to allow easier matching. Is this an appropriate role for the Heart, Lung, and Blood Institute?

Dr. Lenfant. In my view, assisting in the expansion of the registry is an appropriate role for the Institute. The NHLBI has responsibility for research on blood biology and blood diseases, and for the use of blood and blood products and the management of blood resources. Marrow transplantation from related or unrelated donors is a relatively new mode of therapy and there are many aspects that require further research to improve the overall results. The National Marrow Donor Program's registry is a rich research resource because it gives access to data useful for both basic and clinical research that will contribute significantly to the Institute's mission. However, its utility as a national research resource depends on the extent to which potential donors adequately represent certain ethnic and racial groups, and how the samples are collected, typed, and managed. Since our research program is dependent on the availability and quality of the clinical material in the registry and because of our responsibilities in the overall management of blood resources, the Institute is an appropriate partner in the expansion of the registry.

Mr. Natcher. What would this expansion cost in 1991 and how much of this do you think can be raised from private sources?

Dr. Lenfant. To reach the next preliminary goal of 250,000 marrow donors will take more than $11 million for HLA A and B typing alone; adding DR typing, a very desirable option, will double that sum. Based upon past experience, it is reasonable to expect that between $3.0 and $5.0 million can be raised for this purpose from private sources. However, it is hard to convince private sources concerned about a particular patient to provide funds for prospective HLA-DR typing since it doubles the cost and does little to find a donor for that specific patient. It is important to recognize that fund-raising capabilities vary from one segment of society to another, so that it is difficult to be precise in our estimates.

Mr. Natcher. Could your Institute make a grant of this type within the framework of the existing authorizing statutes or would it take a change in the law?

Dr. Lenfant. The Institute uses the research contract mechanism, rather than grants, to support the National Marrow Donor Registry. We feel we have sufficient authority within Title IV, Part C, Subpart 2, which is the authorizing legislation for the Institute, to expand the number of potential donors in the Registry and to assist with the cost of typing needed to facilitate a match. Of course, these contracts are subject to the administrative approvals required by the Federal Procurement Regulations, and the Department of Health and Human Services Procurement Regulations.

HYPERTENSION

Mr. Natcher. Last year this Committee received a lot of letters in support of a large and expensive clinical trial related to mild hypertension. You testified at that time that the Institute was developing less expensive methods to address this issue. What is the status of this project?

Dr. Lenfant. Institute staff has developed a less expensive proposal to answer two of the three main questions posed in the original trial design. The cost of this alternative proposal is estimated at $143 million which is $100 million less than the other trial, but still a significant amount of money. The issue that this trial would address is extremely important.

Hypertension, which affects about 58 million Americans, is a major risk factor for the most commonly encountered forms of heart and blood vessel diseases. It accelerates the development of atherosclerosis of the coronary and peripheral arteries and is the single most important contributing factor to the development of stroke. During the past 20 years, many improvements have occurred in the control of hypertension. The public is more knowledgeable about hypertension, more likely to visit a physician for hypertension, and more likely to follow medical advice. During this same period, there has been a 57 percent decline in the national age-adjusted stroke mortality rate.

The overall health benefits associated with treating hypertension have been well documented. However, studies to determine whether treating mild-to-moderate hypertension reduces heart attacks and deaths from coronary heart disease have produced equivocal results, possibly because of the confounding influence of adverse effects of the drugs used in such studies. New classes of drugs have been increasingly recognized as possible approaches for initial treatment of mild hypertension, but there has not been a conclusive study of their comparative effectiveness. A recent report in the hypertension literature noted that "...large scale trials have not used newer antihypertensives such as calcium antagonists and angiotensin converting enzyme inhibitors. There are no comparable data for these widely used drugs, and we urgently need large scale comparative trials to assess the role of these agents as first line treatments in mild hypertension."

The NHLBI proposes to initiate a clinical trial to compare new antihypertensive medications with current therapy to determine whether the newer approaches are capable of achieving a reduction in the number of nonfatal heart attacks and the mortality from coronary heart disease. The total duration of the trial, including planning, intervention, follow-up of 7-9 years per patient, and data analysis, will be 12 years. Estimated first-year costs are $2.6 million; estimated total costs are $143 million.

CHOLESTEROL EDUCATION PROGRAM

Mr. Natcher. How much money is budgeted for the cholesterol education program in 1990 and 1991?

Dr. Lenfant. The Institute looks at the total amount available for all its education programs rather than focusing on a budget for the individual education programs. At present, the Institute divides the amount available for education programs into two funding pools. One pool of funding is allocated so that a specific sum of money is identified with each of our several education programs. The second pool of funds supports several or all of the education programs. Included in this pool are crossover initiatives such as multiple risk factor education efforts, initiatives implemented at the worksite, and initiatives that target special populations such as those directed toward a specific minority group. Staff salaries and related support costs are also included in this second pool. It is not possible to attribute accurately the costs in this pool to a specific education program.

Costs that are specifically identifiable with the National Cholesterol Education Program are $1,435,000 in FY 1990 and $1,362,000 in

FY 1991. The overall budget for the Institute's education activities, including the National Cholesterol Education Program, National High Blood Pressure Education Program, NHLBI Smoking Education Program, National Asthma Education Program, National Blood Resources Education Program, and National Heart Attack Alert Program is $5,736,000 in FY 1990 and $6,056,000 in FY 1991.

STAFFING LEVELS

Mr. Natcher. Are you satisfied with your current staffing proposal?

Dr. Lenfant. The 1991 request includes a full time equivalent (FTE) employment level of 855 for NHLBI, an increase of 13 FTEs over the 1989 level and 21 FTEs over FY 1990. This level will allow the Institute to carry out ongoing activities and anticipated new requirements.

UNMET NEEDS

Mr. Natcher. I know you have many competing needs but what would you identify as your largest unmet need in 1991?

Dr. Lenfant. Given additional funds, the Institute's first priority would be the restoration of reductions to its existing research centers. These research centers provide a unique opportunity for basic and clinical scientists from a variety of disciplines to collaborate on research in a particular disease area. It should be remembered that the NHLBI is an Institute with a focus on specific clinical conditions, and a large measure of its success comes from the rapid translation of research findings to the bedside. The centers program is critical to that effort because it is uniquely and often exclusively the Institute's avenue for clinical research in a given disease area. The program ensures that advances in basic sciences are translated rapidly into clinical application and that clinical needs provide direction for the basic sciences. Over the years, work performed in the Institute's centers has contributed directly to the betterment of public health through improvements in the prevention, diagnosis, and treatment of disease. Recent research has produced enormous gains in our understanding of fundamental disease mechanisms that can rapidly be translated into new therapeutic interventions. The centers program is the NHLBI's best instrument for achieving that evolution.

ASTHMA PROGRAM

Mr. Natcher. Has there been a shift of funds to the asthma program to reflect the extent and severity of this problem?

Dr. Lenfant. Yes, the Institute has shifted some of its funds to asthma research and education. For example, the NHLBI launched a new National Asthma Education Program in recognition of the growing prevalence of asthma in the U.S. and increasing mortality. Funds were reprogrammed in FY 1989, since the implementation of this new program was a high priority for the Institute.

The Institute will begin a very important initiative in FY 1990 on asthma control in minority children. The primary objective of this initiative is to stimulate demonstration and education research to develop, implement, and evaluate interventions to meet the needs of minority children with asthma inorder to achieve long term control of this condition. The importance of this initiative is illustrated by the fact that morbidity and mortality caused by asthma are higher among blacks. In fact, asthma deaths have been reported to be 350 percent higher than the general population, and hospitalization rates have been reported to be 150 percent greater.

Overall, funds for asthma research are estimated to increase slightly from $16,916,000 in FY 1989, to $17,400,000 in FY 1990, to $18,100,000 in FY 1991.

RESEARCH TRAINING

Mr. Natcher. Do you have any statistical or other empirical evidence that a stipend increase will actually affect who chooses a research career?

Dr. Lenfant. Our Task Force obtained data from the Association of American Medical Colleges (AAMC) on the most current levels of housestaff salaries to use as a guide in determining recommended levels of stipend support for National Research Service Awards (NRSA) trainees. It was a concern of the members of our Task Force, a concern that was verified by the AAMC data, that the existing NRSA stipend schedule could serve as a disincentive to newly trained clinicians who might consider a research career. NRSA stipends were uniformly below the salaries available to housestaff with comparable years of training, with the disparity being particularly pronounced for individuals who might wish to enter into research training immediately following completion of medical school. The Task Force recognized that many newly trained clinicians emerge from medical school with significant levels of personal indebtedness and realized that individuals who elect to pursue clinical careers are likely to receive higher annual incomes and to receive them sooner than individuals who choose to pursue research careers. Because of the substantial disparity between anticipated lifetime earnings associated with clinical and research careers, we believed it to be particularly important to revise the NRSA stipend schedule so that individuals who elect to enter research training do not also have to accept lower remuneration than they would receive if they pursued uninterrupted clinical training.

Mr. Natcher. As far as we can tell, the 1991 budget does not include any increase in stipends. Why isn't a cost of living adjustment included for these grants?

Dr. Lenfant. Within the funds available in the President's Budget, a decision was made to maintain the number of trainees rather than increase stipend levels.

CLINICAL TRIALS

Mr. Natcher. How much money is budgeted for clinical trials in 1989, 1990, and 1991?

Dr. Lenfant. The National Heart, Lung, and Blood Institute obligated $53,681,000 for Institute-initiated clinical trials in FY 1989, and is estimating $59,482,000 in FY 1990 and $48,327,000 in FY 1991.

PREVENTION ACTIVITIES

Mr. Natcher. Dr. Lenfant, your Institute spends a considerably larger portion of its resources on prevention activities including public education. Are you continuing this emphasis in 1991?

Dr. Lenfant. The Institute, through its Office of Prevention, Education, and Control (OPEC), will continue its emphasis on education programs and activities in FY 1991, and will obligate about $6 million for this purpose. The Institute and its advisory committees feel strongly that these education programs are an effective way to promote health and prevent disease because they speed the transfer of information of immediate benefit to the health of the American people. Therefore, OPEC plans to continue its operation of comprehensive national programs in professional, patient, and public education.

Three programs deal with cardiovascular disease: the National High Blood Pressure Education Program, the National Cholesterol Education Program, and the NHLBI Smoking Education Program. In addition to these, the Institute conducts the National Blood Resource Education program and the newly formed National Asthma Education Program. We are also analyzing the feasibility of starting a National Heart Attack Alert Program which would focus on the rapid identification and treatment of heart attack victims, with the goal of reducing morbidity and mortality.

INTRAMURAL RESEARCH

Mr. Natcher. If you are not increasing staff, why does spending in the intramural program increase so rapidly?

Dr. Lenfant. The Institute has allocated additional funds to intramural research in order to take advantage of emerging research opportunities, to increase staffing levels, and to meet rising fixed costs of this research. The intramural AIDS research program is scheduled to receive more than $2.2 million for research on the role of gene therapy in preventing HIV infection, and the role of parvovirus in causing anemia in HIV-infected patients. Included in the budget request are funds for 10 additional FTEs for AIDS research. Also, the President's Budget provides additional funds and two FTEs to more fully develop the cardiac energetics laboratory, which is scheduled to begin its clinical research this Fall. Finally, approximately $2.6 million is provided for mandatory increases in centrally provided services.

CONSTRUCTION

Mr. Natcher. Your budget does not include funds for construction which I believe is authorized for your Institute. Is this a high or low priority for the Institute if additional funds were given to you to spend as you see fit?

Dr. Lenfant. In our professional judgement, there is a need for construction and renovation associated with the acquisition of sophisticated research facilities and instrumentation required by modern biomedical research both within the Institute and within the scientific community that the Institute serves. Therefore, construction would be a high priority when allocating any additional funds that may become available.

Various studies have identified the following critical needs for construction and renovation in the scientific community; (1) mandated safety standards for biohazards (AIDS, virus research) and animal welfare standards, (2) maintenance and repair of existing program facilities, (3) program enhancement in areas of national priority such as AIDS, and (4) new facilities for research in "Developing Institutions." These needs were confirmed at the Research Facilities Construction Conference, held February 9-10, 1988, at NIH, the results of which were reported to Congress.

Above and beyond these general purpose requirements, the NHLBI has specific construction needs tied directly to institute initiatives. Upgraded research facilities and sophisticated research instrumentation are required to implement new research technology in the area of molecular biology. The intramural research program has several new initiatives that require upgraded facilities, including state of the art magnetic resonance imaging in the area of cardiac energetics, gene replacement therapy, pulmonary complications of AIDS, and bone marrow transplantation.

ASTHMA

Mr. Natcher. What can you tell this Committee about recent increases in the incidence of asthma in this country?

Dr. Lenfant. Asthma is a serious chronic disease affecting more than 10 million Americans. During the period 1979 to 1987, the percent of the population with asthma increased by one-third. Rates have increased for all age, sex, and race subgroups. This increased prevalence has had an impact on health care utilization and expenditures. In 1987, asthma was the primary diagnosis for 450,000 hospitalized patients; nearly 15 million asthma-related physician visits took place, and the annual cost of asthma health care exceeded $4 billion. Even though mortality from asthma is low compared to chronic diseases such as heart disease and stroke, morbidity from asthma exacts a large physical, emotional and economic toll on patients and their families. Asthma accounts for well over 100 million days of restricted activity each year.

The racial disparity in asthma deaths is significant and continues to increase. In 1979, blacks were about twice as likely as whites to die from asthma. By 1987, the asthma death rate was almost three times greater among blacks than among whites. This year, the National Heart, Lung, and Blood Institute initiated a special program on "Control of Asthma in Black and Hispanic Children" to examine some of the special problems related to the control of asthma in the minority populations in this country.

In an effort to improve the early detection, treatment and management of asthma, the Institute launched a National Asthma Education Program in March 1989. Modeled on the successful National High Blood Pressure and National Cholesterol Education Programs, over twenty professional and lay organizations interested in asthma are represented on the coordinating committee to plan program objectives, set goals and disseminate information about asthma. Because nearly one-third of the people who suffer from asthma are school age, a major focus of the National Asthma Education Program will be targeted to this group to try to reduce hospitalizations and school absences and increase the understanding of school personnel about asthma and its management.

CARDIAC RISK FACTORS FOR OLDER PATIENTS

Mr. Natcher. Your statement indicates that you have initiated a new study on cardiac risk factors for older patients. This may be of interest to some of the other Members. What can you tell us about this new initiative?

Dr. Lenfant. The Cardiovascular Health Study (CHS) is a population-based study of coronary heart disease and stroke in adults 65 years and older. The main objective of the study is to identify factors related to the onset and course of coronary heart disease and stroke. CHS is designed to determine the importance of conventional cardiovascular disease risk factors in older adults, and to identify new risk factors in this age group, especially those that may be protective and manageable. Considerable attention will be paid to perception of health status and life changes associated with aging. The study design calls for enrollment of 1,250 men and women in each of four communities with both rural and urban populations. Interviews and physical and laboratory evaluations are being performed at baseline to identify the frequency and severity of risk factors, and the presence or absence of disease. The first of two examination cycles began in June 1989. A second comprehensive examination will be repeated three years later.

BRONCHOPULMONARY DYSPLASIA

Mr. Conte. I understand that B.P.D. is a major cause of death in infants who have respiratory distress and were treated by mechanical ventilation. At the current rates, it may surpass cystic fibrosis as the leading cause of chronic lung disease in children. Doctor, what exactly is B.P.D. - broncho-pulmonary dysplasia?

Dr. Lenfant. Bronchopulmonary dysplasia (BPD) is a major respiratory complication seen in newborns who have received mechanical ventilation. First recognized about twenty years ago, BPD involves abnormalities in the architecture of the lung that lead to poor gas exchange and, in many instances, progressive respiratory failure. BPD affects approximately 8,000 infants per year in the United States. Infants with BPD account for the greatest proportion of physical, financial, and emotional morbidity in survivors of neonatal intensive care, including excessively prolonged hospital stays, need for home oxygen administration, and repeated hospitalizations. Just the initial hospitalization for new cases in this country costs over $25 million per year. Not included in this conservative estimate are costs associated with treating recurring pulmonary infections and other long term problems that are common in BPD survivors. Clearly, this is a major medical and economic problem.

Mr. Conte. What research are you doing that looks at the underlying mechanism of B.P.D. and ways we can better treat this disease among newborn infants?

Dr. Lenfant. Currently, the major proportion of research on BPD is supported through the Specialized Centers of Research (SCOR) program "Respiratory Disorders of Neonates and Children." SCOR investigators are seeking to define the sequence of events that lead to BPD and chronic lung injury in premature infants. The National Heart, Lung, and Blood Institute is supporting studies to elucidate the genetic control of enzymes that protect lung cells against oxygen damage, in the hope that this will eventually lead to interventions to prevent or ameliorate the oxygen-induced lung injury seen in infants with BPD. Investigators are exploring the possibility that replacement therapy with surfactant, a vital substance missing from lungs of premature infants, will prevent or lessen the severity of BPD in premature infants. Recent studies suggest that vitamin A supplementation may reduce the incidence and severity of BPD in premature infants; clinical studies to evaluate the potential of this promising approach are now in progress. The Institute is seeking to expand its research programs in BPD through a new initiative to investigate cellular and molecular events associated with lung injury in premature newborns during the first few weeks of life. If this new program is initiated, it has the potential to make significant contributions towards understanding basic mechanisms of BPD, and lead to new approaches towards its prevention and treatment.

PRIMARY PULMONARY HYPERTENSION

Mr. Conte. Dr. Lenfant, primary pulmonary hypertension is a rare but deadly disease which often strikes younger women. What is known about this disease?

Dr. Lenfant. It is true that primary pulmonary hypertension is a rare and deadly disease which most often occurs in young women 20 to 40 years of age. The cause of this disease is unknown, except for an outbreak of over 70 cases which occurred in Europe about 20 years ago and was traced to the ingestion of an appetite suppressant. The most common early symptoms are difficulty in breathing, fatigue and fainting. The course of the disease varies widely, but the majority of patients live 2 to 3 years following the time of diagnosis. Approximately 25 percent survive longer than 5 years. The small blood vessels in the lung become obstructed, preventing the flow of blood through the lungs. As the disease progresses, heart failure develops because the heart is unable to pump blood through these obstructed vessels.

Mr. Conte. What are the future directions for research into primary pulmonary hypertension?

Dr. Lenfant. The National Heart, Lung, and Blood Institute recently completed a national registry of patients with primary pulmonary hypertension. The purpose of the registry was to collect and analyze data on the cause, natural history, and treatment of this disease. Approximately 200 patients were enrolled and were followed for as long as five years. Studies of the lung tissue from these patients demonstrated that one of the primary reasons the lung blood vessels close off is because of abnormal growth of tissue in the vessel wall. A new direction of research is trying to identify factors that inhibit the growth of tissue in the normal vessel wall, as well as to look for factors that may be causing the abnormal growth in the diseased vessels. Research on primary pulmonary hypertension has been limited because all attempts to develop an animal model of the disease have been unsuccessful.

Mr. Conte. Are you looking at drugs that might help to open up these blood vessels?

Dr. Lenfant. In a multicenter clinical trial, a drug called prostacyclin is currently being evaluated experimentally for the treatment of primary pulmonary hypertension. The trial was initiated and is being supported by the private sector. Because patients with primary pulmonary hypertension have irreversible structural changes in the blood vessels, studies supported by the Institute are focussed on attempting to identify what is causing this abnormal growth of the vessel wall. Once the mechanism is better understood, there will be an opportunity to develop drugs to control the growth of the vessel walls.

GLUTATHIONE AND AIDS

Mr. Conte. I heard that your institute found a substance called glutathione which is critical for the functioning of the immune system.

Are you doing research to see whether replacement therapy of this compound could help AIDS patients?

Dr. Lenfant. Patients with HIV infection do have reduced levels of the anti-oxidant glutathione. Recent intramural research has shown that administration of aerosolized glutathione safely increases the levels of glutathione in the lungs. The efficacy of this treatment has not been established, however. Our investigators are now seeking a biological assay for tissue function that might serve to assess whether patients are helped. The FY 1991 budget includes funds to expand this research.

ALPHA-1-ANTITRYPSIN DEFICIENCY

Mr. Conte. Alpha-1-antitrypsin deficiency is a serious cause of emphysema. I hear that Dr. Crystal at your institute is looking at genetic therapy techniques that could revolutionize treatment of this disease. Can you share with us how genetic therapy would work in this type of emphysema?

Dr. Lenfant. Alpha-1-antitrypsin deficiency can now be treated by replacement therapy in which aerosolized alpha-1-antitrypsin is periodically administered to the lungs. As a genetic disease, it is an excellent candidate for potential gene therapy. One approach would be to use the retroviral gene transfer methodology developed by Dr. Crystal in the intramural division, to transfer the human alpha-1-antitrypsin gene into T-lymphocytes obtained from the patient and then to re-administer the T-cells to the patients. This is very similar to the procedure developed by another or our researchers, Dr. F. Anderson, and used successfully in the first gene transfer experiments in human patients (the TIL protocol).

Experiments already done demonstrated that T-lymphocytes, which do not normally synthesize alpha-1-antitrypsin, can be genetically modified to secrete this protein and that genetically modified cells transplanted into mice augment the levels of alpha-1-antitrypsin in the serum and fluid in the epithelial lining of the lung. It may also be possible to genetically modify the T-lymphocytes so that they would preferentially accumulate in the lungs, or they might be administered directly to the lungs. In this way, high local concentrations of alpha-1-antitrypsin could be attained locally where it is most needed without increasing the levels elsewhere in the body.

CARDIAC ARRHYTHMIAS

Mr. Conte. Doctor, abnormal cardiac rhythms afflict millions of Americans. Some are more troublesome than others. What is the scope of your research that looks into abnormal heart rhythms?

Dr. Lenfant. The Institute supports a broad research program on abnormal heart rhythms that includes both intramural and extramural research. Over the past two years, the intramural cardiology branch has established a clinical electrophysiology laboratory that is dedicated to understanding the arrhythmic (abnormal heart rhythm) basis of sudden cardiac arrest and/or death and loss of consciousness in certain high-risk subgroups of patients. In particular, a great deal of effort has been devoted to elucidating mechanisms for the events in patients with a familial form of heart muscle disorder called "hypertrophic cardiomyopathy". This cardiac disorder frequently causes unexpected and sudden death in young individuals who are otherwise asymptomatic and fully active. Studies in the electrophysiology laboratory are also an essential part of efforts to identify the genetic defect(s) in hypertrophic cardiomyopathy because characteristic electrophysiologic abnormalities can occur in patients who appear symptomatically normal.

Within its extramural program, the Institute supports a number of grants which study mechanisms involved in the genesis of abnormal cardiac rhythms (arrhythmias). These studies are in three categories: disorders of impulse formation, disorders of impulse conduction and disorders of both impulse formation and conduction. Of necessity, such studies must be done in animal models. They involve research into the movement of potassium, calcium and sodium ions and into the structure and function of the proteins involved in these ion movements, as well as the metabolic activity of the cells that generate the electrical impulse. Studies of how the electrical current passes from cell to cell are equally complex. Any one investigator can only study a small portion of these interrelated activities. Studies of disorders which lead to arrhythmias must be built on the foundation of how electrical impulses are generated and are propagated through heart tissue under normal circumstances. So, in addition to the disease-oriented grants, we support other grants where the aim is to develop fundamental understanding of the pacemaker and conduction system of the heart.

The Institute also funds studies of various drugs which can affect electrical impulse generation and conduction and the mechanisms by which they exert their effects in the heart. Recent advances in molecular biology and immunology now allow investigators to determine the precise stage at which these drugs act and why they sometimes have unexpected side effects. The Institute supports a clinical trial of such antiarrhythmic drugs and a study of removal of a focus of abnormal electrical activity using a catheter. Our Specialized Centers of Research also include a small number of clinical studies of arrhythmias, specifically, those related to patients who have had heart attacks. We have under consideration the development of a Specialized Center of Research program on sudden cardiac death, a condition which involves arrhythmias and which results in about two hundred fifty thousand deaths each year.

Mr. Conte. What is the significance of E.P.S. research in looking at the different kinds of "heart blocks" and other abnormal rhythms?

Dr. Lenfant. Electrophysiological studies (EPS) involve the use of electrodes placed through catheters at various sites on the heart to diagnose cardiac rhythm disorders and to evaluate the efficacy of drugs used to treat the disorders or to determine the need for pacemaker implantation. Such procedures are only used after noninvasive tests have failed to yield a diagnosis. Most often these studies are used to diagnose unexplained palpitations or fainting, which may have their origins in several different parts of the heart's electrical conduction system.

Experience with EPS in the study of arrhythmias associated with coronary heart disease has shown that successful diagnosis may depend on the event which precipitated the arrhythmia. For example, if oxygen deprivation was the initiating event, EPS might not identify a patient at risk. The usefulness of EPS lies in the ability of the physician to reproduce the type of rhythm disorder that the patient has experienced outside the laboratory.

PCR TECHNOLOGY

Mr. Conte. What has been some of the major applications of the PCR technique at your Institute?

Dr. Lenfant. The development of the polymerase chain reaction (PCR) is one of the most substantial technical advances in molecular genetics in the past decade. The procedure is able to amplify discrete portions of impure and complex mixtures of DNA in a simple and automated fashion. It is sensitive, specific, and rapid. For example, beginning with a single molecule of DNA, PCR can generate 100 billion similar copies in one afternoon. Moreover, the ability to generate a large number of copies from minute quantities of impure starting materials enables the investigator to study DNA from fixed pathological specimens, a single cell, or a drop of blood.

In our research program, the major applications of PCR fall into two broad categories - research applications and medical applications. In terms of the former, PCR is potentially useful in any situation that requires the examination of DNA. Hence, it is used to supplement or enhance techniques to study the structure, function, and regulation of the genome as it pertains to the normal and abnormal function of the cardiovascular, pulmonary, and hematologic systems. For example, PCR was used to isolate and characterize a gene for a novel growth factor of vascular cells, to study the structure and activation of a gene important to dissolving blood clots, to identify genes responsible for abnormalities in lipid metabolism and to define their role in atherosclerosis.

In terms of medical applications, diagnostic procedures have profited greatly from PCR because infections or genetic diseases are characterized by the presence of either foreign or aberrant DNA. Hence, rapid and sensitive procedures exist to detect sickle cell anemia, Beta-thalassemia, hemophilia A and B, cystic fibrosis, and alpha-1 antitrypsin deficiency. PCR can be used to insure a safe supply of blood by detecting the presence of trace amounts of infectious agents, such as HIV and hepatitis B virus, to identify the infectious agents in certain forms of myocarditis, and to determine the infectious etiology of pulmonary disorders such as herpes simplex pneumonia.

Investigators working in cystic fibrosis research have already capitalized on the diagnostic capabilities of PCR technology to identify the multiple rare mutations that are apparently present in this genetic disease. Using PCR, researchers have screened DNA from cystic fibrosis patients and their relatives for the most common mutations. Research laboratory teams are also searching for alternative mutations causing cystic fibrosis by combining data derived from sequence analysis of the recently identified cystic fibrosis gene and PCR technologies. So far twenty-two multiple rare mutations have been found. This information is essential in order to initiate programs for early detection of cystic fibrosis and in the search for the cause of this fatal disease.

Mr. Conte. What areas of heart, lung and blood research will stand to gain the most from this technique?

Dr. Lenfant. Due to its ability to amplify specific DNA sequences enormously in a very short period of time, PCR will continue to have a valuable impact in disease diagnosis. Since a single cell provides enough material for analysis, PCR will have a strong impact on pre-natal diagnosis. Apart from its value in rapid diagnosis, PCR will prove highly useful in studying the pathogenesis of heart, lung, and blood diseases because of its ability to detect specific DNA sequences that can be correlated with defined pathologic conditions. PCR will also greatly facilitate tissue typing to match transplant donors and recipients. In addition to direct medical applications, PCR allows the investigator to perform DNA manipulations that are difficult or impossible with standard molecular biological approaches. For example, PCR provides new options in molecular genetic studies for adding genetic information to target materials or for altering what is already there.

TPA VERSUS STREPTOKINASE

Mr. Conte. Doctor, there is a report out of Europe that says that T.P.A. - that new clot-buster drug for heart attacks - is not all that much better than "~~strep-toe-kinase~~ STREPTOKINASE" and is very expensive. Others are saying the study did not take into account the new recommendations to front-load the dosages during a heart attack. Could you comment on this study?

Dr. Lenfant. The study you refer to was carried out in Italy and involved 12,000 heart attack victims randomized to two treatment strategies. The first using streptokinase, a first generation clot-dissolving drug, which is inexpensive and the second strategy involving tissue plasminogen activator (tPA), a second generation clot-dissolving drug manufactured by recombinant DNA techniques, which is much more expensive. The Italian investigators report that there was no difference in mortality between the two drugs during the hospital stay. Although the results have not been published in peer review journals the study seems to have been well conducted and the conclusions reasonable. Some critics have noted that the design of the study included giving heparin to half of each randomized group beginning 12 hours after entry to the study and that this may have resulted in less effective tPA action. In addition, others have noted that more rapid infusion of tPA results in improved reopening of arteries. There is a second international study, designed to compare three thrombolytic agents--streptokinase, tPA and anistreplase with an anticipated sample size of 60,000 patients that will be quite important in helping cardiologists select a first line drug. Results are expected in 1991. The Institute believes that the Italian study contributes important information. However, it leaves untested the hypothesis that a treatment including tPA with concomitant administration of heparin might result in improvements in mortality compared to a treatment with streptokinase and heparin.

Mr. Conte. Is TPA too expensive for what it does?

Dr. Lenfant. The current price for tPA to hospitals is $2,200 per treatment, which is much more expensive than the first generation agent streptokinase. If the Italian study results are confirmed and accepted, cost considerations might dictate that tPA be reserved for those instances where streptokinase could not be used, such as in patients who have recently received streptokinase. Streptokinase is a bacterial protein that elicits antibody formation potentially leading to allergic reactions during the second administration.

EDUCATION PROGRAMS

Mr. Conte. What is your Institute doing to inform health care professionals and the public about the prevention of coronary artery disease and the latest treatment of heart attacks?

Dr. Lenfant. The Institute has three national educational programs directed toward the primary prevention of coronary artery disease: The National High Blood Pressure Education Program, the National Cholesterol Education Program, and the NHLBI Smoking Education Program. These programs have been educating professionals, patients, and the public about identification and control of risk factors for coronary artery disease.

Primary prevention is clearly important, but for those in whom primary prevention has failed or has come too late, acting to minimize the effect of heart attack by preserving cardiac muscle is of paramount importance. In order to achieve this goal, it is essential to minimize the time from the first symptoms and signs to treatment action. Early action is essentially a three-phase process: 1) recognition of the symptoms and signs requiring action by the victim and those in his/her environment, 2) action prior to arrival at the hospital or emergency center, and 3) action upon arrival at the hospital or emergency center. Recent advances in therapy, especially from clinical trials evaluating thrombolytic therapy, suggest that impressive reductions in morbidity and mortality in heart attack patients are associated with the use of such therapy.

The NHLBI has initiated planning for an educational effort to reach key groups with relevant messages and actions concerning identification and treatment of patients with acute myocardial infarction (heart attack) at each of the three phases. The new educational effort has been tentatively titled the National Heart Attack Alert Program. A symposium is being held this fall to address the significant issues related to such a program and to advise the Institute about how it should proceed.

CONSTRUCTION GRANTS

Mr. Conte. Doctor, when was the last time your institute received construction grant funding?

Dr. Lenfant. In FY 1987, the NHLBI awarded $2,250,000 for extramural construction grants.

Mr. Conte. Is there a need for such grants?

Dr. Lenfant. Yes, although they were not as high a priority as research grants, construction grants for new biomedical research facilities or the improvement of existing facilitites in the extramural community is important to address a variety of needs.

Mr. Conte. What opportunities might be available if the grants were provided in the budget?

Dr. Lenfant. If construction grants were provided, the heart, lung, and blood research programs would be enhanced in a number of areas. Construction of facilities would allow a broadening of the science base by establishing facilities for research programs at the cutting edge, for example, molecular biology. These awards would also permit institutions to deal with physical deterioration through normal use and aging, and to meet new regulatory standards affecting animal care, laboratory practice, and health, safety, and environmental issues. We believe that the productivity of our research programs would be greatly enhanced if the research facilities were improved.

HYPERTENSION

Mr. Conte. Sixty million Americans suffer from hypertension. Forty million of these have "essential hypertension" - persistent high blood pressure with no known cause. I hear that I.L.-2 has been found to be effective in lowering blood pressure in animals. What is the current status in looking at I.L.-2 in humans?

Dr. Lenfant. In a study carried out at the Masonic Medical Research Laboratory in New York, investigators reported that a single dose of interleukin-2 (IL-2) normalizes blood pressure up to a year in a particular strain of rats. This strain is widely used as an animal model for human essential hypertension, that is, where the cause is unknown.

Mr. Conte. What are the prospects for its use as an anti-hypertensive drug?

Dr. Lenfant. Since IL-2 alters the immune response, the implication from these preliminary studies is that essential hypertension may be caused in part by a defect in the immune system. At this point, it is premature to state that a defective immune system is one of the major causes of hypertension. It is important that these studies first be reproduced by other investigators.

It is difficult to know if the effect of IL-2 on spontaneously hypertensive rats can be extrapolated to humans, especially since hypertension is a multifactorial disease that is due to a variety of genetic and environmental factors. In the end, carefully controlled human studies will be necessary to evaluate the utility of IL-2, or other immune system agents, for the treatment of human hypertension. However, at this time, we believe that the observation from the Masonic Medical Research Laboratory has opened a very interesting new avenue of research.

HEMOPHILIA

Mr. Conte. Doctor, hemophilia is a difficult, painful disease. Not only do people suffer from the disease itself, but it also puts them at risk for other diseases associated with blood products - hepatitis, AIDS, and several others. Are there some new approaches in the treatment of hemophilia?

Dr. Lenfant. Newer approaches to the treatment of hemophilia rely almost exclusively on the techniques of molecular biology and gene therapy. Of these approaches, one in particular, holds special promise because of the potential for treating both hemophilia A and B. It has been known for some time that two complementary pathways of blood clotting exist within the body. In one pathway, factor VIII and factor IX are required. Blood from patients lacking these important proteins takes unusually long to form clots. But coagulation can also occur by a second pathway which is independent of factor VIII and factor IX. The approach to which I refer, bolsters this alternate means of blood clot formation by infusing factor VII, a key protein of the alternative pathway. Human recombinant factor VII is now available. First shown to be effective in controlling hemorrhages in hemophilia A patients who had developed antibodies to infused factor VIII, and therefore derived no benefit from factor VIII replacement therapy, recombinant factor VII has subsequently been shown to correct the bleeding defect in hemophilia A patients without inhibitors and in hemophilia B patients. Purity, lack of infectious agents, and ease of administration make recombinant factor VII an attractive form of therapy. A Phase 2 clinical trial with recombinant factor VII is in the planning stages.

A second promising approach to the treatment of hemophilia is that of gene therapy. Recently investigators have succeeded in developing a mouse model of factor IX somatic cell gene therapy. The gene for this clotting protein was incorporated into normal mouse cells in tissue culture. When these cells were placed into mice, they began secreting factor IX in levels which would have been sufficient to convert a case of moderate hemophilia B to a much milder form. Ultimately, correction of the genetic defect in hemophilia using gene therapy shortly after birth is likely to be possible. Such an approach should prevent the clinical manifestations and disabling complications of this disease in affected individuals.

LIFE-STYLE AND CLOGGED ARTERIES

Mr. Conte. A recent study said that strict changes in diet and life-style can actually reverse clogging of the arteries. If the data checks out, what would be the implications of this research?

Dr. Lenfant. Lifestyle and behavioral influences account for the majority of coronary heart disease morbidity and mortality. Epidemiologic and clinical studies suggest that atherosclerotic lesion development and progression can be influenced by smoking, diet, exercise and stress. Currently, interventions in coronary atherosclerosis worldwide rely on lipid lowering drugs to modify the progress of atherosclerosis progression, and surgical or invasive procedures such as angioplasty and coronary artery bypass to improve myocardial perfusion. However, these treatments do not halt or reverse the underlying propensity for disease, which stems from lifestyle. -

The most recent data on reversal of coronary atherosclerosis through a comprehensive, non-drug lifestyle modification program has significant implications for the health care system. For individuals with acknowledged coronary heart disease, this treatment regimen offers a non-pharmacological, non-surgical alternative to regaining their health through an intensive regimen of diet, stress management, moderate exercise and smoking cessation. At present, one cannot isolate the effects of the individual components, although the study director considers the combination of diet and stress management to be most strongly associated with disease reversal.

These findings also open potential avenues for disease prevention by considering how this admittedly stringent program could be modified to increase acceptance by the general population. As coronary heart disease is still the number one source of morbidity and mortality in this country, the development and testing of such preventive strategies are of the highest priority in this Institute. Should the follow-up results demonstrate continued and consistent positive findings, namely reduced lesion size and increased coronary blood flow and perfusion with definitive impact on morbidity and mortality, a large scale clinical trial may be needed to determine if such a treatment program could be successfully undertaken by a broad cross-section of coronary heart disease patients and treatment facilities across the country. Encouraging the development and testing of a preventive program for the general population would also be given high priority.

Mr. Conte. What role does stress play in the development of atherosclerosis?

Dr. Lenfant. The thrust of the evidence from various types of research on stress, from animal studies as well as human studies, is that blood cholesterol levels increase rapidly during a variety of stressful experiences.

In animals, including monkeys, stress has been shown to accelerate atherosclerosis even in the absence of a high cholesterol diet. However, not all monkeys are equally vulnerable. Monkeys which exhibit high cardiovascular reactivity to stress develop atherosclerosis more quickly, possibly because of the added influence of a high heart rate, which also tends to complicate matters. Highly reactive monkeys also release greater amounts of stress hormones into the blood stream, which interact with cholesterol. Although such experimental studies cannot be conducted in humans for ethical reasons, human observational research has consistently supported the reactivity-atherosclerosis association which has been experimentally demonstrated in animal models. Preliminary evidence suggests that reducing such reactivity has an inhibiting effect on the development of atherosclerosis, but further research is required to better understand the dimensions and validity of this relationship.

ARTIFICIAL LUNG DEVICES

Mr. Conte. New devices are being made that could help failing lungs. The intravascular oxygenator (IVOX) is one such device. Can you tell me how artificial lung devices might help some patients?

Dr. Lenfant. The intravascular oxygenator (IVOX) is a new, experimental artificial lung device that is inserted into the body's central vein. The device pumps oxygen through tiny, membranous tubes, allowing the exchange of oxygen and carbon dioxide with blood as the blood flows over the tubes. The idea of using membrane oxygenation to augment natural lung function in patients with the Adult Respiratory Distress Syndrome has existed for many years. The underlying assumption for these devices is that resting the lungs, by allowing the device to perform part of the work of gas exchange, will enable them to recover so that they will be able to resume effective gas exchange. However, experience has proven membrane oxygenator therapy to be only a short term solution. The underlying lung injury must be prevented or cured if the patient is to recover and, therefore, more basic research on the nature of acute lung injury is needed. One of the most important uses of membrane oxygenators may be to support critically ill patients who are awaiting a lung transplant. As the number of lung transplants increases, there will be an increased need for short term respiratory support for these patients, some of which might be provided by these devices.

Mr. Conte. What are some of the key difficulties involved in developing an artificial lung?

Dr. Lenfant. A major difficulty in developing an artificial lung is the biocompatibility of the device; blood clots form easily on the surface of the membrane. As a result, the patients require anticoagulant therapy and are prone to serious bleeding complications. Many investigators are experimenting with new synthetic polymers to coat the tubing. Bonding anticoagulant heparin to the surface of the tubing may be another means of reducing these complications. Another biocompatibility problem is that platelets may be destroyed by internal forces as they pass through the device. This could further compromise the patient's coagulation system. Finally, the membrane provides a good substrate for bacteria which may lead to massive systemic infections.

Another challenge is the design of the device itself. The human lungs are ingeniously designed with a surface area of 70-80 square meters, about the size of a football field, containing tiny capillaries of approximately 10 microns in diameter; they are able to oxygenate up to 20-25 liters of blood per minute. The devices in current use have a surface area of less than a single square meter with considerably larger "capillaries"; they can only oxygenate up to 2.5-3.0 ml of blood per minute. Scientists continue to look for an improved design which may lead to more efficient function.

ARTIFICIAL BLOOD

Mr. Conte. If we can develop a synthetic blood, we would go a long way towards reducing the incidence of hepatitis, AIDS, and other blood borne diseases associated with transfusion. We could save billions of dollars. What is your Institute doing in the field of synthetic blood development?

Dr. Lenfant. The Institute has long recognized the need for blood substitutes. The research supported by the Institute has as its primary objective the development of safe, non-toxic, and inexpensive products capable of performing certain functions of blood. Most substitute research involves two different types of products, namely, perfluorochemical compounds, and hemoglobin-based substitutes, both of which function as red blood cell substitutes. In addition, there is considerable research activity in the commercial sector to develop oxygen-carrying substitutes. Many of the products being developed employ hemoglobin molecules from human red blood cells as oxygen carriers. One product is currently being evaluated in a small clinical trial. Since the supply of human red cells is limited, some manufacturers have turned to animals such as cattle, as sources of hemoglobin. Some very recent scientific developments supported by the Institute that are particularly exciting employ genetic engineering techniques in which microorganisms and laboratory animals have been used to produce human hemoglobin. It will take several years of intensive research to determine whether these potential substitutes will be safe and effective for replacement therapy in humans.

HEPATITIS C

Mr. Conte. Last year, scientists discovered the virus that causes hepatitis C. What has your Institute been doing in hepatitis C research?

Dr. Lenfant. Since the cloning of the hepatitis C virus (HCV) genome, an assay to detect antibodies to HCV has been developed using genetic engineering techniques. The Institute participated in the evaluation and validation of the assay by providing investigators with thousands of coded specimens from its repository of blood samples collected in earlier prospective studies of posttransfusion hepatitis. The results obtained suggest that HCV is the major cause of posttransfusion hepatitis and that antibody to HCV is detected in approximately 85 percent of infected individuals with evidence of chronic hepatitis, and about one-fifth of those chronically infected develop cirrhosis of the liver. Thus, the emergence of a specific test for HCV, expected to be licensed by mid-1990, should have a major impact in preventing posttransfusion hepatitis. The NHLBI is currently developing a research initiative to determine the incidence of posttransfusion hepatitis after implementation of the new assay by the blood banking community.

Mr. Conte. What are the prospects of developing interferon as a treatment against hepatitis C?

Dr. Lenfant. In spite of current screening procedures, thousands of blood recipients contract posttransfusion hepatitis annually. The long-term consequences of the disease represent a serious public health problem. Two recent clinical trials provide some hope for patients suffering from chronic hepatitis C, previously termed non-A,non-B hepatitis. These studies showed that administration of interferon, produced by genetic engineering techniques, induced remission in about half of a group of patients with chronic hepatitis. Discontinuation of interferon therapy, however, resulted in relapse in most individuals. Further studies are necessary to understand the effects of interferon therapy in patients suffering from chronic hepatitis C.

Mr. Conte. What is the National Blood Resource Education Program doing to prevent the spread of hepatitis C?

Dr. Lenfant. As part of its mission to improve the safety and adequacy of the Nation's blood supply, the National Blood Resource Education Program (NBREP) has begun a vigorous educational campaign to increase the appropriate utilization of blood and blood products. Two NBREP expert panels addressed indications for the appropriate use of red blood cells, platelets, and fresh frozen plasma, as well as the use of autologous (patient's own) blood. Those reports are being widely distributed to physicians and other health professionals. Physicians are encouraged to use blood only when therapeutically necessary, thus minimizing patients' exposure to donor blood and any risk of contracting infectious diseases such as hepatitis C virus (HCV). Moreover, autologous blood transfusion is the treatment of choice for appropriately selected patients. Exclusive or supplemental use of autologous blood can reduce or eliminate many transfusion reactions and exposure to transfusion-transmitted viruses.

This spring, HCV tests will be licensed by the Food and Drug Administration and will be used to screen all blood and blood components collected for transfusion. The HCV screening test will greatly diminish the risk of transmitting the hepatitis C virus via blood transfusions. However, it will continue to be important to educate physicians and other health professionals about the therapeutic indications for using blood and the appropriate use of autologous blood to minimize patients' risks.

PEDIATRIC CARDIOLOGY

Mr. Conte. Congenital cardiac defects are a major cause of pediatric illnesses. What has been some of the key accomplishments of your Institute in the field of pediatric cardiology?

Dr. Lenfant. The incidence of congenital heart disease is about eight per thousand live births. A major accomplishment of the Institute has been the support of research leading to better diagnosis of cardiac defects in infants and children. This has enabled surgeons to plan procedures with greater confidence and thus reduce the time the patient spends under anesthesia and cardiopulmonary bypass. Further Institute supported research on diagnostic techniques has resulted in accurate methods for detection of heart defects in the fetus while still in the mother's womb. This enables pediatric cardiologists to plan the care of the patient before birth. It is estimated that about thirty-three percent of pregnant women now undergo echocardiography of the fetus, for detection of heart defects. About sixty percent of heart defects are now detected before birth. A fundamental issue concerns the way in which congenital heart defects develop since this is believed to involve both genetic and environmental factors. The Institute has issued three requests for applications to study the embryologic development of the heart and to identify mechanisms which are perturbed when congenital heart defects arise. We also support a program project in this area and we have established a Specialized Center of Research in Congenital Heart Disease, which was initiated on January 1, of this year.

The Institute has also sponsored fundamental research aimed at improving the outcome of heart surgery in infants and children. Current research is helping to define the composition of solutions that are used to arrest immature and maturating hearts during surgery. A further problem concerns the cardiopulmonary bypass equipment used during surgery. It is believed that interactions between blood and the materials used in the apparatus may contribute to post-surgical complications in babies and children. The Institute is about to issue an initiative to study the fundamental mechanisms involved in this interaction and to devise means to prevent possible deleterious effects. Another complication following some surgery has been disturbed heart rhythm. Institute supported studies have contributed to a considerable reduction in the number of patients who suffer this condition and to better treatment for patients who still experience them.

CHOLESTEROL MEASUREMENTS

Mr. Conte. Your Institute is leading the way with your National Cholesterol Screening Program. This is a great way to educate the public about the importance of knowing your cholesterol number. However, there have been concerns over the accuracy of the screening devices being used. What is your education program doing to assure accurate readings of the people being tested?

Dr. Lenfant. An important part of identifying and treating people with high blood cholesterol is precise and accurate measurement of

cholesterol levels. To address this issue, the National Cholesterol Education Program (NCEP) formed an expert panel which issued recommendations to improve laboratory performance and to promote the optimum use of the laboratory by physicians. Detailed recommendations for more reliable cholesterol values are also provided for manufacturers of analytical instruments and diagnostic reagents, clinical laboratory workers, and those using desktop analyzers. It should be noted that the measurement of blood cholesterol can be done very accurately, as the experience of NHLBI research over a decade has shown. The NCEP's treatment guidelines call for repeated measurements before a treatment program is initiated, and this helps safeguard the accurate classification of cholesterol levels. The tools are available for making necessary improvements in accuracy, and conscientious efforts by physicians and laboratories, in accordance with NCEP guidelines, can produce accurate results.

In recognition of the great interest in public cholesterol screening, which has been spurred by the availability of portable desktop analyzers, the NCEP recently issued guidelines on conducting high quality public screening. Recommendations are provided on quality control, accuracy of results, training of staff, the environment of the screening, information provided to those screened, and proper referrals to physicians for follow-up. It is noteworthy that the Department's Inspector General has strongly recommended that these guidelines be followed by all.

DIET AND CHILDREN

Mr. Conte. What is currently known about the relationship between diet in children and future incidence of heart disease?

Dr. Lenfant. The evidence relating dietary fats, blood cholesterol levels, and coronary heart disease (CHD) is derived from many different types of research approaches. So far as human studies are concerned most of these have been conducted in adults. However, atherosclerosis is generally viewed as a continuous process often beginning in childhood and the clinical consequences of which are nearly always delayed until middle-age or later. Only recently has evidence been available that directly links elevated blood cholesterol and early atherosclerotic lesions in children and very young adults. In adults, it is established that lowering elevated blood cholesterol levels favorably affects development, progression and even regression of atherosclerotic plaques. There are no studies providing direct proof that lowering blood cholesterol in children and adolescents will reduce the risk of CHD when they reach adulthood; however, the available evidence strongly suggests that this is probably true.

The National Cholesterol Education Program's Population Panel recently recommended that children, as they begin to eat with the family, usually at two years of age or older, adopt a dietary pattern that provides about 30 percent of calories from fat and provides fatty acids of less than 10 percent of calories and cholesterol intake of less than 300 mg per day. This recommendation for healthy children is directed toward a long term benefit of a reduction in blood cholesterol in children that would, if carried into adult life result in a substantial reduction in coronary heart disease.

Mr. Conte. What is involved in the Dietary Intervention Study in Children program?

Dr. Lenfant. The Dietary Intervention Study in Children (DISC) is a clinical trial designed to test the feasibility, acceptability, efficacy and safety of a cholesterol-lowering diet in pre-pubertal children, aged 8 to 10 years who have elevated low density lipoprotein (LDL) cholesterol levels. This trial was begun in December 1986, and will be completed in 1993. Six hundred children identified to have high LDL-cholesterol will be enrolled and followed for at least three years to determine if a cholesterol-lowering diet can be followed by children and their families and if this diet can meet the nutritional needs for growth and development in children. Over 450 children and their families have been enrolled thus far and are presently participating in grouped dietary intervention sessions conducted at six clinical centers in the United States.

The adequacy of a cholesterol-lowering diet for the special nutritional needs of growing children is not presently known. The results of DISC should provide much needed information on the long-term efficacy and safety of a cholesterol-lowering diet in children and adolescents, by examining the long-term effects of such a diet on blood cholesterol levels, height, weight, physical and cognitive development, sexual maturation and nutritional adequacy markers.

CENTERS PROGRAM

Mr. Conte. What is the status of your centers program?

Dr. Lenfant. Since 1971, the Institute has supported Specialized Centers of Research (SCORs) to advance basic knowledge and generate techniques and methods of clinical management and prevention in selected areas of heart, blood vessel, lung, and blood research. Currently, 54 centers are supported in 12 topic areas. Since 1972, the Institute has also supported at least 10 Comprehensive Sickle Cell Centers that combine basic and clinical research and clinical trials with application, training, and community service projects.

In regard to the funding status of research centers, the Institute is concerned about a decline in funding since FY 1987 from $87,424,027 to the FY 1991 estimate of $86,295,000. In 1987, the average cost of a center award was $1,457,000. In 1991, it is estimated to be $1,348,000. The funding status of our centers programs has reached a point where the Institute is considering a reduction in the number of centers supported.

Mr. Conte. Given the recommended budget, do you expect that the Institute will need to continue downward negotiations at the Centers?

Dr. Lenfant. Under the 1991 Budget Request, the Institute anticipates center awards will be 24-25 percent below the approved levels.

RHEUMATIC HEART DISEASE

Mr. Conte. Rheumatic heart disease used to be very common in the United States. While the incidence of rheumatic fever has fallen over the years, there are still over two million victims of rheumatic fever and heart disease that are still living.
What has been the latest developments in the treatment of rheumatic heart disease?

Dr. Lenfant. Streptococcal infections, the cause of rheumatic fever, are still very sensitive to penicillin, and this drug continues to be the treatment of choice. Effective prophylactic treatment consists of penicillin administered orally or intramuscularly on a monthly basis for individuals at risk, or erythromycin for those who are allergic to penicillin.

Mr. Conte. What has been the latest developments in the development of replacement valves, often used in these patients?

Dr. Lenfant. The National Heart, Lung and Blood Institute is not supporting any research to evaluate artificial heart valves. Private industry continues to support research and development on new artificial heart valves.

KAWASAKI DISEASE

Mr. Conte. What is Kawasaki disease?

Dr. Lenfant. Kawasaki disease is an acute illness of unknown origin, with deleterious effects on the heart, occurring in infants and young children. Epidemic outbreaks of the disease are seen at two- to three- year intervals. The estimated incidence of Kawasaki disease in the United States is five thousand cases per year, however many cases may be under-reported because Kawasaki disease is often mistakenly diagnosed as measles.

Although the number of cases seen at major medical centers was relatively stable in 1986 and 1987, there is evidence to suggest an increasing incidence of Kawasaki disease since 1988. The frequency and severity of this disease have made it a leading cause of acquired heart disease in children.

Mr. Conte. How does Kawasaki disease affect the heart?

Dr. Lenfant. The most important complication of Kawasaki disease is coronary artery swelling (aneurysm), which when untreated, results in complications in up to thirty percent of cases and an acute fatality rate in the range of one or two percent. In an Institute supported trial, patients treated with aspirin and high-dose gamma globulin had a three-to five-fold reduction in the prevalence of coronary aneurysms, as compared to those who received aspirin alone.

Although most complications regress over time, large aneurysms do not regress, and there is additional evidence that the coronary arteries may develop narrowing or obstruction, leading to heart attack and sudden death. Cardiovascular complications have also been observed in some patients despite treatment, and the late manifestations may be severe. Some older children have required treatment with coronary artery bypass graft surgery or coronary angioplasty because of coronary obstruction from Kawasaki disease. The frequency of these severe late manifestations may be increasing.

Mr. Conte. Is there research being done at your institute to find the cause of this disease?

Dr. Lenfant. NHLBI-supported investigators are attempting to identify the cause of Kawasaki disease. Clinical and laboratory manifestations of Kawasaki disease are consistent with a viral cause. There is preliminary evidence which suggests that the disease may be caused by a retrovirus, although this has not been confirmed. When the cause is definitely established, it may be possible to develop a sensitive diagnostic test which would allow early institution of treatment, as well as determination of the true incidence of this disease. In addition, more rational treatment or prevention of the disease may become possible. In the meantime, NHLBI-supported investigators continue to pursue new developments in the treatment of Kawasaki disease, including a study comparing efficacy of single-dose versus four-day infusion of intravenous gamma globulin.

CYSTIC FIBROSIS

Mr. Conte. What is the Institute doing in the field of cystic fibrosis research?

Dr. Lenfant. Recently, scientists reported that they had discovered the gene for cystic fibrosis, a truly remarkable step forward in our quest to understand and treat this devastating, fatal genetic disease. This recent discovery has availed pulmonary scientists with a powerful new tool to further understand the basic mechanisms underlying this disease. The availability of probes for the gene is already promoting investigations into alternative mutations that may explain the clinical heterogeneity in this disease, for example, why some patients have lung and pancreatic problems while others only have respiratory involvement, and why some have milder forms of the disease while others are more severely afflicted.

Scientists supported by the Institute are analyzing the physiologic function perturbed by the gene product and its localization. A major goal of these studies is to establish how the gene product relates to the ion transport abnormality, characteristic of cystic fibrosis, and to understand the link between the defective ion movement, the thickened mucus, and the propensity to the airway infections so prevalent in this illness. Investigators are trying to develop animal models which are pivotal to understanding the pathophysiology of this disease, as well as to the development of new and more effective therapies. These animal models would form an important adjunct to recently developed in vitro model systems such as the immortalized cells, and would facilitate clinical testing of potential pharmacologic and genetic approaches to therapy.

Mr. Conte. What are some of the promising avenues in C.F. treatment?

Dr. Lenfant. Until now, treatment of lung disease in patients suffering from cystic fibrosis has largely relied on the use of rigorous antibiotic therapy to control dangerous respiratory infections. On the horizon is a promising new therapy employing aerosolized amiloride, a diuretic which inhibits excessive salt and water absorption from airway secretions. Results of a small clinical trial conducted on adult patients indicated the ability of amiloride to slow the disease-induced decline in pulmonary function and to normalize the flow properties of sputum. These findings, if confirmed in a larger clinical trial, should lead to a rapid extension of these studies to explore the effectiveness of this drug in younger children. In the more distant future, the discovery of the gene for cystic fibrosis heralds increased optimism that new approaches to treatment will be forthcoming as a by-product of our increased understanding of the pathogenesis of this fatal genetic disease.

SARCOID AND THE HEART

Mr. Conte. Sarcoid is a major systemic disease that can cause heart failure. What research is being done to look at the effects on the heart by sarcoid?

Dr. Lenfant. Sarcoidosis is a disease that may appear in several organ systems of the body, including the heart. The disease manifests itself primarily as an excessive infiltration of the tissues by white blood cells of the T-helper lymphocyte variety. The effect of this on the heart is to cause interruption of the normal electrical signals that control the heart's rhythms, which may then result in a weakening or irregularity in the heart beat, resulting in heart failure or sudden cardiac death.

Current research in cardiac sarcoidosis has examined the use of chemotherapy to prevent disturbed heart rhythms, together with automatic implantable defibrillators to prevent sudden death. In addition, the drug dipyridamole has been found to reverse some of the heart defects seen in sarcoidosis patients. The Institute supports a program of research in the pulmonary manifestations of sarcoidosis, where particular emphasis is being placed on the activity of T-helper lymphocytes. On further development, these studies may well lead to a better understanding of sarcoidosis, not only in the lungs, but in the heart as well.

DRUGS TOXIC TO THE HEART

Mr. Conte. Some cancer drugs are toxic to the heart. Doxorubicin is one such agent. What research is being done to investigate the mechanisms by which these medications injure cardiac tissue?

Dr. Lenfant. Doxorubicin/adriamycin is a potent, broad-spectrum chemotherapeutic agent effective against certain human malignancies. The dosage of doxorubicin and other anthracycline drugs is severely limited by a chronic cardiomyopathy which occurs most frequently at high cumulative doses. The dosage which leads to life-threatening cardiotoxicity varies considerably among individuals and many patients could likely benefit from levels of this drug that are higher than the current recommended limit. Administration of such higher doses requires careful monitoring of the status of the heart muscle. Currently this is done by endomyocardial biopsy, which is an invasive procedure involving surgical removal of a piece of the heart wall, radionuclide measurement of cardiac ejection fraction, which is an assessment of the functional capacity of the heart, and echocardiography. Scientists are working on development of magnetic resonance imaging as a noninvasive way to monitor the heart which would not involve ionizing radiation. It might also avoid sampling artifacts that can accompany the biopsy procedure and may possibly detect lesions earlier.

Research until now has produced conflicting data regarding the mechanism(s) by which doxorubicin induces myocardial damage. A variety of mechanisms have been proposed including (1) membrane damage leading to changes in transport and permeability and (2) damage to the energy machinery of cells. One such study has shown that metabolites of the drug induce calcium release from isolated heart mitochondria, which are the energy factories of the cell. The most prominent model for toxicity involves the generation of free radicals and activated oxygen species which can damage cardiac lipids and/or sulfur-containing proteins in cell membranes. The latter would be consistent with the ability of certain sulfur-containing reagents to reduce the cardiotoxicity of the drug. Discovery of the mechanism of drug toxicity could lead to the design of protective therapies. One drug currently undergoing clinical trials is ICRF-187. While its mechanism of action is still under investigation, it has been shown to be particularly effective in preventing doxorubicin toxicity.

STROKE BELT INITIATIVE

Mr. Stokes. In your opening statement you discussed briefly the "Stroke Belt" initiative. Please give me an update on this project.

Dr. Lenfant. This year, the Institute will begin a special initiative on stroke that will focus on 11 southeastern states, known as the "Stroke Belt", in which stroke mortality rates are higher than in the rest of the country. The initiative will refocus and increase program efforts toward reducing stroke morbidity and mortality through three components: outreach through churches; a mass media campaign; and funding to stimulate the development of innovative educational strategies. The Stroke Belt initiative will continue to emphasize the role of churches as an avenue to increase public awareness on the need for high blood pressure control and smoking cessation to decrease the risk of stroke. Churches have proven to be especially effective at reaching the black population; in the stroke belt states, blacks have age-adjusted death rates from stroke that are two times higher than the national average. The mass media effort includes a plan to have a state health department representative in each stroke belt state work with radio and television stations on a "Strike Out Stroke" campaign. The NHLBI will work with this team, providing a media package, program materials, lists of spokespersons, and ideas for programming. In return, the stations would make a commitment to deliver the messages over a period of time, thus ensuring consistent delivery in a variety of formats. Media efforts also include disseminating the message through national media that reach black audiences in the stroke belt and across the rest of the country.

In addition, state health departments located in stroke belt states will receive funds to initiate projects that assess high risk target audience needs and identify opportunities for more effective delivery of medical and/or educational services. Four general categories of projects will be considered for funding: 1) problem assessment, 2) evaluation and data analysis, 3) educational interventions, and 4) community organization techniques. The information obtained from these projects will be utilized for future broad-scale program planning and development activities of the National High Blood Pressure Education Program.

NATIONAL MARROW DONOR PROGRAM

Mr. Stokes. What are the risks involved to both the donor and the recipient of bone marrow?

Dr. Lenfant. Donating marrow is not trivial or innocuous. A prospective donor must donate two to four units of blood for later autologous use to replace the volume in one to two quarts of marrow and blood that is withdrawn. The procedure is done in the operating room under general or spinal anesthesia. Many donors spend only one night in the hospital after the donation and most are home and back to near normal activities within three days. There are no long-term consequences of donating marrow. No marrow donor under the National Marrow Donor Program has had any serious consequence from the marrow donation itself, probably in part because of the great care taken in being certain that the donation poses no undue risk to the donor. A very small number of marrow donors that are related to the recipient have suffered serious, though not permanent problems as a result of the donation.

Marrow transplant recipients are prepared to receive the marrow by destroying their own marrow and immune system, usually with a combination of radiation and chemotherapy. This preparatory regimen is lethal without a subsequent transplant. During the period between the destruction of the recipient's own marrow and the beginning growth of the transplanted marrow, the recipient is nearly defenseless against bacterial and viral infections. They also must receive transfusions of red blood cells and platelets to replace those normally made by the marrow. Marrow donors are often screened for both common and rare virus infections. As the transplanted marrow begins to grow, it can react against the host-recipient, producing acute, or later chronic graft-vs-host disease which results in dysfunction of multiple organ systems.

Mr. Stokes. How much is requested to support the bone marrow registry in FY 1991?

Dr. Lenfant. For FY 1991, $3.9 million is requested for the support of the National Marrow Donor Program.

Mr. Stokes. How does this compare to FY 1990?

Dr. Lenfant. The Institute has allotted $3.6 million for the support of the National Marrow Donor Program during FY 1990.

EDUCATION PROGRAMS

Mr. Stokes. Last year, Congress made a special effort to provide additional funds for your public education programs. Will they be in danger again this year under the President's Budget?

Dr. Lenfant. The Institute's education programs are not in danger, but we will need to make difficult choices about which activities we pursue. The FY 1991 request provides a small increase over the 1990 estimate for the Institute's education programs. However, we are reevaluating the situation and will make every effort, including reprogramming, to keep these programs at the FY 1989 level of $7.3 million.

Mr. Stokes. How much is requested for them?

Dr. Lenfant. The FY 1991 President's request includes $6,056,000 for NHLBI education programs.

MINORITY RELATED RESEARCH

Mr. Stokes. How much of your extramural program is devoted to minority related research?

Dr. Lenfant. In FY 1989 the NHLBI provided $69.8 million for funding of research related to minorities, approximately 7.6 percent of the Institute's extramural funds. In FY 1990, we estimate that we will obligate $79.8 million for minority-related research, which is 8.5 percent of the extramural component of the budget.

Mr. Stokes. How much would the figure be under the FY 1991 request?

Dr. Lenfant. The estimate for minority-related research at the FY 1991 request level would increase to $83.4 million. This represents approximately 8.6 percent of the Institute's extramural component of the President's Budget.

Mr. Stokes. What are you doing in the area of AIDS and minorities?

Dr. Lenfant. The National Heart, Lung, and Blood Institute's AIDS program has several high priority programs specifically targeted to minorities. These include the following: a program to study cardiac and pulmonary complications in infants and children with human immunodeficiency virus (HIV) infection; a program to study the pulmonary complications in HIV infected drug abusers; and, a program to investigate the possible therapeutic effects of HIV-hyperimmune globulin in infants infected with HIV. The ultimate objective of all these programs is to improve treatment. Brief descriptions of these follow:

Minority infants and children constitute one of the most rapidly growing groups of HIV infected individuals in this country. Pneumocystis carinii pneumonias and lymphoid interstitial pneumonia are major complications in this group. Yet these disorders have not been well investigated and many questions remain unanswered. Frequent cardiac abnormalities have also been demonstrated in infected adults, but the incidence and clinical course of these abnormalities in infants and children have not been delineated. A group of studies on the pulmonary and cardiac complications of HIV infection is currently investigating the natural history, and optimal treatment of these disorders. Eighty percent of the group under study is expected to be minority.

Immune globulins are naturally occurring antibodies in the blood that are essential to combat infection. The use of supplemental immune globulins for the prevention of a variety of viral and bacterial infections is well documented. Several investigators have reported that the amount of antibodies in the serum of HIV-infected individuals, which are specifically directed against HIV, correlated with disease stage and progression. Based on these data, several scientists believe that the infusion of immune globulin, containing specific antibody against HIV, into HIV-infected individuals would maintain adequate immune function and prevent progression of disease. Accordingly, the NHLBI plans to conduct clinical tests to evaluate the efficacy of infused immunoglobulin as a treatment of HIV infection. The initial trial will test the efficacy of immune globulin in infants infected with the virus and will be performed in conjunction with NIAID and Abbott Laboratories. Because infants infected with the virus are primarily minorities, the study population is expected to be more than 80 percent minority. If results are promising, further studies will be planned. Furthermore, if successful, this program will augment the effort to produce a vaccine against HIV.

Pulmonary complications of HIV infection is an extensive program designed to study the natural history of lung disease in the HIV infected population. A major arm of this study is examining drug abusers exclusively and its patient population is expected to consist of more than 90 percent minorities.

In addition, the Institute is supporting a large number of projects which will benefit the minority population. The Institute is keenly aware of the disturbing shift of AIDS into the minority community and are involved in the process of developing medical approaches to combat this epidemic.

MINORITY INVESTIGATORS

Mr. Stokes. I understand that NHLBI has a special initiative that would increase the number of minority investigators. Please tell me about this program.

Dr. Lenfant. The Institute has developed not one, but several programs to increase the number of minority investigators participating in biomedical research, although individuals from minority groups can compete for any of the mechanisms of support available through the Institute. Summarized below are some of the minority-specific programs implemented to encourage minority faculty and potential researchers to develop research skills in areas related to heart, lung, and blood diseases.

Research Supplements for Underrepresented Minorities Program attracts minority investigators and potential minority investigators to careers in heart, lung, and blood research by providing supplemental funds to active research grants supported by the NHLBI. The program includes three initiatives: the Minority Investigator Research Supplements; the Minority Graduate Research Assistants Supplements; and the Minority Undergraduate Research Supplements. In FY 1989, the NHLBI funded 30 percent of all the research supplements supported by the NIH.

Biomedical Research Enhancement for Minority Schools (BREMS) is the newest NHLBI initiative to increase the number of minority investigators. It provides research training opportunities in the NHLBI intramural research program to junior and tenure-track faculty from minority health professions schools.

The Preventive Cardiology Academic Award (PCAA) offers opportunities to foster research and careers in the prevention of heart disease and improve the quality of preventive cardiology curricula. This fiscal year the eligibility criteria for this program was modified to encourage applications from minority medical schools and from medical schools providing physician training to a significant number of underrepresented minorities.

The Minority School Faculty Development Award encourages the development of faculty investigators at minority schools in areas related to cardiovascular, pulmonary, and hematologic research by offering faculty the opportunity to enhance their research capabilities in these areas.

The Minority Institutional Research Training Program (MIRT) offers research training for graduate students, health professional students, and postdoctoral students enrolled at minority schools, who are willing to take time off from their studies and who have the potential to develop a meritorious program in cardiovascular, pulmonary, or hematologic research. Participation in this program strengthens these scientific disciplines in the minority institution.

The NHLBI also actively participates in the Minority Biomedical Research Support (MBRS) and the Minority Access to Research Careers (MARC) programs. The NHLBI is constantly exploring new ways to recruit and train minorities for careers in biomedical research and these programs offer another avenue to achieve this goal.

SICKLE CELL DISEASE

Mr. Stokes. What progress has been made in the area of sickle cell disease?

Dr. Lenfant. There have been major accomplishments in sickle cell disease in the past decade. Significant advances have been made at the cellular and molecular levels on the role of the red cell membrane, alterations in blood flow and the increased adherence of sickle cells to endothelial cells to enhance our understanding of the underlying problems of sickle cell disease. Basic research has improved our knowledge of how genes can be manipulated by drugs and other molecular mechanisms to trigger fetal hemoglobin production, thereby ameliorating the symptoms in patients with sickle cell disease. This promising approach has become the centerpiece of clinical investigations with agents such as hydroxyurea and the hematopoietic growth factor, erythropoietin.

New drug therapies can be designed and tested in recently developed laboratory mice with red blood cells that contain human sickle hemoglobin. The application of new transgenic technology to the development of a mouse model containing the sickle globin gene is a major advance for investigating sickle cell disease in vivo. Such a model permits studies that cannot be carried out in patients and should further our understanding of the pathogenetic mechanisms of sickling disorders.

Genetic studies have identified four separate mutations in patients with sickle cell disease, distributed geographically in different parts of Africa and Asia. Sickle cell anemia can now be classified according to these mutations and correlated with specific complications. The ability to classify and predict clinical severity is essential for selecting various therapies. For this reason, the Institute is seeking to develop a clinical severity index to use in making treatment decisions based on an analysis of clinical and genetic data available. If successfully developed, this index will greatly assist treatment decisions.

Mr. Stokes. The Cooperative Study of Sickle Cell Disease has been going on since 1979. What have we learned from this study?

Dr. Lenfant. Our research investment in the Cooperative Study of Sickle Cell Disease has produced significant results. This prospective study has provided a unique opportunity to document what happens to patients with sickle cell disease from birth through adulthood. From the study of this large group of over 4,000 patients, the incidence and outcome of a number of acute and chronic complications have been determined and the management of these problems has greatly improved. Important data has emerged on the influence of sickle cell disease on growth and development, confirming the delay in weight, height and sexual maturity. As the result of this clinical study, clinicians can now define by non-invasive techniques how the spleen loses function during the first year of life, contributing to the increased susceptibility to infections.

A major finding documented unequivocally the benefit of prophylactic penicillin in preventing pneumococcal infections and early deaths in infants and emphasized the need for newborn screening. This study, by carefully monitoring deaths, has established more definitively the ages of greatest risk of deaths and their causes in pediatric patients in this country. Analysis of mortality data of young patients during the first eight years has added an important optimistic outlook, showing improved survival in patients under the age of twenty, as compared to previous reports.

Further studies will continue to yield important data on clinical events. For example, we know that the symptoms in patients with sickle cell disease vary significantly, and range from mild to very severe. The ability to classify and predict clinical severity is essential for determining patient selection for various therapies. For this reason, the Institute is seeking to develop a clinical severity index to use in making treatment decisions based on an analysis of clinical and genetic data available from this study. If successfully developed, this index will prove to be extremely valuable in treatment decisions.

RESEARCH GRANTS

Mr. Early. What percentage of approved grants would be funded under the FY 1991 budget request?

Dr. Lenfant. We estimate that 25.8 percent of approved grants will be funded under the FY 1991 budget request.

Mr. Early. How does this compare to FY 1990 and FY 1989?

Dr. Lenfant. In FY 1990 the National Heart, Lung, and Blood Institute plans to fund 22.0 percent of approved grants; in FY 1989 the Institute funded 27.9 percent of approved grants.

Mr. Early. When was the last time the award rates were as low as these?

Dr. Lenfant. The 1990 award rate is the lowest the award rates have been.

Mr. Early. How much has the award rate decreased over the past 10 years?

Dr. Lenfant. In FY 1982 the award rate was 37.2 percent and in FY 1991 the award rate is expected to be 25.8 percent. This is a decrease of 11.4 percentage points between 1982 and 1991, but the decrease is 15.2 percentage points between 1982 and 1990.

Mr. Early. What about your payline? Give us some idea of where the FY 1990 and FY 1991 percentile puts the payline.

Dr. Lenfant. With regard to raw score payline, raw scores are no longer used for allocating funds. NIH has decided to use either percentile payline data or award rates. The award rate is the percent of approved grants funded out of the total approved grants eligible for funding. A very rough calculation of raw score payline is 160 for FY 1990 and 120 for FY 1991.

At the time we prepared the budget, we expected to pay to the 14th percentile in FY 1990 and to the 16th percentile in FY 1991. Our experience with the grant applications that have been reviewed to date indicates that we may be able to achieve a payline in FY 1990 at the 16th percentile or perhaps higher.

Mr. Early. NHLBI seems to have another year of rather significant reductions. What effect will another year of reductions this size have on the research project grants?

Dr. Lenfant. We think the effect will be significant, but it is difficult to assess the precise impact of the downward negotiations in research grants on the research project grants of the Institute.

Mr. Early. What effect will another year of reductions have on the research conducted on grants?

Dr. Lenfant. The magnitude of the reductions we have implemented the past few years have forced investigators to cut back the scope of their planned research activities. This reduction in scope has had the effect of slowing research progress.

RESEARCH CENTERS

Mr. Early. What effect will downward negotiations have on these centers and their research programs?

Dr. Lenfant. Under the 1991 President's Budget, the Institute anticipates center awards will be 24-25 percent below the approved levels. The anticipated downward negotiations will undoubtedly affect the ability of the Institute's centers to carry out research at the planned level. A common result of budget reductions is to reduce the scope of the proposed research. Given the highly integrated design of the centers programs, any reduction in workscope can be expected to have a multiplying effect on all aspects of the program. Further, in the clinical research area, budget reductions may reduce the number of patients that can be studied as well as the number of control subjects. These effects would tend to slow the progress of research in the scientific area addressed by the program.

These reductions also hamper the ability of individual centers to collaborate with each other in the planning and execution of clinical, epidemiologic, or treatment studies that require a multicenter effort. Finally, diminished budgets would limit the capability to provide training environments in which young scientists, particularly physicians, may gain important research experience.

Mr.Early. What is the estimated full cost for research centers in FY 1991?

Dr. Lenfant. The estimated total cost for NHLBI's research centers FY 1991 is $114,096,000.

Mr. Early. Doctor, did the Institute request any new centers for FY 1991?

Dr. Lenfant. Yes, the NHLBI did request funds for an additional center in FY 1991 in its preliminary budget.

Mr. Early. If so, for what areas?

Dr. Lenfant. The NHLBI believes we need to fund a Specialized Centers of Research in vascular biology, sudden cardiac death, and heart failure.

While the incidence of symptomatic peripheral vascular disease approached that of coronary artery disease and the number of invasive procedures performed on peripheral vascular tissue approaches the number of surgical procedures involving the coronary artery, the therapeutic success for peripheral vascular disease has been less impressive than for coronary artery disease. A SCOR program in vascular biology would serve to focus research on obtaining a comprehensive knowledge of the mechanisms involved in maintaining normal peripheral artery structure and function and in the pathophysiology of vascular disease.

Sudden cardiac death claims over 270,000 Americans annually and accounts for about 50 percent of all deaths from coronary artery disease. Yet, the mechanisms triggering the lethal arrhythmia remain obscure. Basic knowledge about electrical activity in cardiac tissue has been developed, but has yet to provide leads directly applicable to the clinical event. The Institute believes that the multidisciplinary, collaborative atmosphere of a new SCOR program will provide the impetus to translate basic electrophysiologic studies into clinically useful diagnostic and therapeutic approaches as well as foster the pursuit of new knowledge. Recent reports of an association between circadian rhythm and sudden cardiac death similar to that demonstrated for myocardial infarction provide clues to the pathophysiologic events precipitating a lethal arrhythmia. The new SCOR in Sudden Cardiac Death would pursue these research avenues.

A new SCOR in Heart Failure will address a condition that currently affects about 2.3 to 3.8 million Americans and is becoming an increasing problem as the population ages. For most patients with heart failure, therapy is palliative; the only treatment available for end-stage heart failure is a heart transplant. The NHLBI continues to pursue vigorously a number of therapeutic strategies, such as treatment with vasodilator drugs and the development of the artificial heart. Nonetheless, it is apparent that success in the clinical area depends on the existence of a parallel effort in basic research. At present, very little is known about the underlying mechanisms of heart failure. The relative roles of changes in gene expression, receptor regulation, ion channel and pump maintenance, and metabolic activity in myocardial dysfunction are poorly understood. Further, there are many unanswered questions about the mechanisms whereby cardiac myocyte necrosis occurs as a result of changes in structure and function of the heart and the coronary circulation. New knowledge of the pathophysiology, biochemistry, and molecular biology of heart failure will lead to improved strategies for the clinical care of patients with this condition.

Mr. Early. Did you request funds to expand existing centers in FY 1991?

Dr. Lenfant. Yes, funds were requested in the FY 1991 preliminary budget to restore ongoing centers to their full cost and to expand the number of ongoing center programs. Additional centers were requested for our ongoing centers programs in cystic fibrosis, cardiopulmonary disorders of sleep, thrombosis, transfusion medicine and hypertension.

Mr. Early. Why did you feel new and expanded centers were warranted?

Dr. Lenfant. The Institute's Specialized Center of Research (SCOR) program supports research on related important topics where a concentration of research resources, facilities, and personnel permit a multidisciplinary approach to research problems. The centers provide a unique opportunity for basic and clinical scientists from a variety of disciplines to collaborate on research in a particular disease area. The NHLBI is an Institute with a focus on specific diseases, and a large measure of its success comes from the rapid translation of research findings to bedside medical practice. The centers program is critical to that effort, because it is the Institute's often exclusive avenue for clinical research in a given disease area. The SCOR program ensures that advance in basic sciences are translated rapidly into clinical application and that clinical needs provide direction for the basic sciences. Over the years, the research of the SCOR programs has contributed directly to the betterment of public health through new approaches to prevention, diagnosis, and treatment of disease.

CLINICAL TRIALS

Mr. Early. Doctor, will you have to curtail any ongoing clinical trials with your FY 1991 budget request, and if so, which ones?

Dr. Lenfant. The NHLBI intends to make every effort to fully fund trials already underway. Clinical trials are carefully designed to enroll a critical number of patients within a certain amount of time. To apply reductions to these trials could jeopardize the entire study. Therefore, we will review carefully each one to see if cost savings are possible. If we are not able to identify savings, we will redirect funds from another source.

Mr. Early. Are there any high priority clinical trials which are ready but cannot be initiated because of lack of funds in the FY 1991 request?

Dr. Lenfant. Yes, we have several clinical trials we would like to initiate if funds become available.

Mr. Early. If so, please provide a list of these, along with a brief description and the associated costs, including first year cost.

Dr. Lenfant. If funds were available, the Institute would support the following new clinical trials:

1. Children's Activity Trial in Cardiovascular Health
   The overall goal of this trial is to measure and compare the effects of school-based interventions for promoting long-term healthful behavior in elementary school children and adolescents to reduce their subsequent cardiovascular disease risk.

Mechanism: Research Contract
Duration: 9 Years
First Year Cost: $6,000,000
Total Cost: $42,000,000

2. Coronary Heart Disease in High Risk Hypertensives
This randomized clinical trial will test whether antihypertensive drug treatment with representative drugs from classes recently adopted for initial treatment, can reduce the incidence of clinical coronary heart disease, compared to standard drug treatment.

Mechanism: Research Contract
Duration: 12 Years
First Year Cost: $2,100,000
Total Cost: $143,100,000

3. Childhood Asthma Management Program
This trial will determine whether an intervention program for children with asthma, which includes stepped-care drug therapy to maximize lung function and educating patients and parents to better manage the disease, can significantly improve growth of lung function, decrease utilization of health care resources and limitation of activity, and enhance school performance.

Mechanism: Research Contract
Duration: 9 Years
First Year Cost: $875,000
Total Cost: $40,000,000

4. Effect of Digitalis on Survival in Patients with Congestive Heart Failure
This clinical trial would be to determine the effect of digitalis on mortality in patients with congestive heart failure and whether digitalis treatment prevents worsening of heart failure.

Mechanism: Research Contract
Duration: 7 Years
First Year Cost: $200,000
Total Cost: $6,500,000

5. Hyperglycemia as a Risk Factor for Cardiovascular Disease
The objectives of this initiative are to assess the effect of differing degrees of hyperglycemia on: conventional cardiovascular disease risk factor levels such as lipids and blood pressure; alterations in lipoprotein and apoprotein concentrations including possible measurements of glycosylation of apoproteins; and alterations in platelet functions and blood clotting factors. The study also will compare the distribution of cardiovascular disease risk factors in males versus females with various degrees of glucose intolerance.

Mechanism: Research Project Grant
Duration: 4 Years
First Year Cost: $777,000
Total Cost: $3,327,000

6. Antiarrhymics and Beta-Blockers Study
Sudden death is the most common cause of death in congestive heart failure patients. A trial is necessary to assess whether antiarrhythmic agents are effective in patients with poor ventricular function, and whether beta-blockers are as useful in this population as in those without failure.

Mechanism: Research Contract
Duration: 8 Years
First Year Cost: $2,000,000
Total Cost: $45,000,000

7. Management of Elevated Blood Pressure in Children
Children with blood pressure elevations consistently between the 90th and 98th percentile for their age and height would be randomized into a trial comparing one or more specific dietary interventions such as low sodium diet, weight loss, and/or increased potassium with no treatment. Pharmacologic treatment would be initiated for those not responsible in the intervention group. Endpoints would include such measures as lowering of relative blood pressure change with age, change in 24-hour blood pressure patterns, change in left ventricular mass, and/or measurement of vascular resistance in various sites.

Mechanism: Research Contract
Duration: 8 Years
First Year Cost: $2,300,000
Total Cost: $24,000,000

8. Treatment of Idiopathic Fibrotic Lung Disease
This trial will be designed as a randomized double blind intervention study comparing high dose corticosteroids with lower dose corticosteroids and cyclophosphamide.

Mechanism: Research Contract
Duration: 6 Years
First Year Cost: $1,000,000
Total Cost: $30,000,000

9. Membrane-Active Agents to Prevent Sickle Cell Disease
As new membrane-active agents are developed for treatment of various disorders, particularly heart disease or high blood pressure, it appears promising that some of these agents may alter the ion balance in red blood cells and prevent sickling and shape change in cells containing sickle hemoglobin. This study will test the effectiveness of these drugs in a population of

sickle cell patients who are refractory to all other forms of therapy.

Mechanism: Research Project Grant
Duration: 3 Years
First Year Cost: $500,000
Total Cost: $3,000,000

10. Transfusion Therapy for Prevention of Recurrence of Stroke in Sickle Cell Disease
The objective of this trial is to determine if four years of standard transfusion therapy following a stroke in young patients with sickle cell disease is sufficient to prevent recurrence of stroke in these patients.
Mechanism: Research Contract
Duration: 8 Years
First Year Cost: $750,000
Total Cost: $9,668,000

11. Sleep Apnea Intervention Study
The basic goal of the proposed study would be to critically test the hypothesis that reduction or elimination of recurrent airway obstruction during sleep (with nasal CPAP) does decrease morbidity and alter the short term natural history of the obstructive sleep apnea syndrome. A second hypothesis is that obstructive sleep apnea is associated with systemic hypertension and that relief of the airway obstruction improves or eliminates the sleep apnea associated systemic hypertension.

Mechanism: Research Contract
Duration: 6 Years
First Year Cost: $1,782,000
Total Cost: $13,036,000

12. Peripheral Vascular Disease
The objective of this trial would be to assess whether or not interventions in people with symptomatic peripheral vascular disease (PVD) results in reduction in coronary heart disease, for which this population is at high risk.

Mechanism: Research Contract
Duration: 11 Years
First Year Cost: $1,000,000
Total Cost: $58,000,000

Mr. Early. To what extent are NHLBI clinical trials supported through the centers program?

Dr. Lenfant. The Institute does not use the research centers mechanism to support clinical trials. Our clinical trials are large scale, controlled studies of human subjects which have a well-defined experimental protocol and a precisely-stated prospective intervention, the results of which may be expected to serve as validation of the effectiveness of a proposed preventative or therapeutic regimen. These trials are more appropriate to the cooperative agreement and research contract mechanisms. However, clinical investigations are of course, an essential component of all centers, and many small-scale experimental human studies are supported. For example, the Specialized Center of Research (SCOR) in Arteriosclerosis at the University of California, San Diego, includes a study of low doses of protocol in patients with familial hypercholesterolemia, in an attempt to determine the anti-oxidant properties of the drug; and the SCOR in Coronary and Vascular Disease at Johns Hopkins University is making a study of alternative forms of circulatory support in victims of cardiac arrest, to look for improvements in survival and neurological status, by comparison with standard therapy. These studies are not large scale, population-based trials.

Mr. Early. What effect will large downward negotiations have on clinical trials?

Dr. Lenfant. Large downward negotiations normally cannot be made on large clinical trials because large reductions would change the nature of the project being supported forcing alterations in the protocol or the number of subjects enrolled in the trial. For this reason, the Institute carefully reviews its cooperative agreement and research contract supported clinical trials to see if any reductions can be taken. If not, these trials are often made exceptions to the reductions policy.

EDUCATION PROGRAMS

Mr. Early. Doctor, the institute conducts a number of education and prevention programs. What are your plans in this area for FY 1990 and FY 1991?

Dr. Lenfant. The Office of Prevention, Education, and Control continues to operate comprehensive national programs in professional, patient, and public education. Recent activities in these programs range from development of definitive treatment guidelines for health professionals to production of mass media public service advertising campaigns. In FY 1990, work is underway to define treatment guidelines for high blood cholesterol in children and adolescents. A major effort in the high blood pressure area is the development and implementation of a special initiative, called "Strike Out Stroke (SOS)," to reduce stroke in the 11 southeastern states which form the "Stroke Belt", a region having a higher stroke mortality rate than the rest of the country. A special focus of this effort will be community programming and mass media strategies to reach the black population, since blacks in the Stroke Belt are twice as likely to die of stroke as whites in that region. Smoking education activities will continue the theme of "clinical opportunity", which means developing tools to help health professionals more effectively intervene with patients who smoke. A new national education program was launched just one year ago. The National Asthma Education Program was begun in recognition of the growing prevalence of asthma in the U.S. and increasing mortality. The program is working on production of definitive guidelines for asthma diagnosis and treatment for physicians and other health professionals.

In FY 1991, many of OPEC's current activities will be continued and intensified, and the possibility of new programs will be explored. For example, the asthma program has initiated a collaborative effort with the Department of Education to reach school administrative and health personnel. Broader collaboration in school health education is being considered for FY 1991, especially in light of new recommendations on cholesterol-lowering in children and adolescents. In addition, NHLBI is analyzing the feasibility of starting a National Heart Attack Alert Program, focusing on the rapid identification and treatment of heart attack victims, with the goal of reducing morbidity and mortality.

Mr. Early. Doctor, how much will be allocated for prevention and education programs in FY 1990 and how much does your FY 1991 request include?

Dr. Lenfant. The 1990 estimate for the Institute's national education programs is $5,736,000. At the FY 1991 request level, $6,056,000 has been included for education programs.

Mr. Early. Are you proposing increases in any of these programs in FY 1991?

Dr. Lenfant. The FY 1991 request level provides an increase of $320,000 over the 1990 estimate before reprogramming.

Mr. Early. Are the funds in the budget request adequate to carry out the task at hand?

Dr. Lenfant. The NHLBI currently sponsors five major science-based health education programs. The recent addition of two new programs, the National Blood Resource Education Program and the National Asthma Education Program, has required the Institute to make difficult decisions concerning resource allocations. To date, needs have been partially met through more focused planning and improved management techniques. However, the Institute has now reached a point where it can no longer add any additional program activities. Due to the importance of several recently recognized needs related to our educational activities, the Institute has submitted a request to reprogram funds into this area in 1990. The addition of a program such as a National Heart Attack Alert Program, currently under consideration, is dependent upon the extent to which additional funds become available. Also, the expansion of the newest national education program on asthma awaits an infusion of funds to meet the many special areas of need and the many target groups we plan to reach.

Mr. Early. What should we be doing that we are not now doing?

Dr. Lenfant. The coordinating committees of each of our educational programs, and the Ad Hoc Committee on Minority Populations, have recommended numerous program initiatives and innovative approaches that address the many critical issues confronting us in our efforts to effectively reach professionals, patients, and the general public with information on the prevention and control of diseases of the heart, lungs, and blood. Unfortunately, every year many of these excellent ideas must be deferred while others cannot even be considered. In many of our programs we would like to do more to reach minorities and others who have been traditionally underserved.

I have been most pleased with the efforts of our National High Blood Pressure Education Program's Stroke Belt initiative which has focused a mix of program activities in states in the southeastern U.S. that have experienced extremely high stroke rates. The program is currently working with 12 state health departments to implement a Strike Out Stroke media campaign and is funding contracts to them that will provide the means to develop new educational approaches to better meet the needs of high risk populations. Programs patterned after this type of intensified approach must await the available of additional resources. NHLBI also sponsors an annual workshop with representatives from all the state health departments; with additional funds, the Institute could offer follow-up assistance and meet the large demand for assistance to state and community efforts in initiating new programs in cardiovascular and pulmonary disease prevention and control.

PEDIATRIC AIDS

Mr. Early. How much has been allocated for pediatric AIDS in FY 1990 and FY 1991?

Dr. Lenfant. In FY 1990, $4.3 million has been allocated for pediatric AIDS. This amount increases to $5.1 million in FY 1991.

USES FOR ADDITIONAL FUNDS

Mr. Early. If an increase over the FY 1991 request is provided, how would you use these additional funds?

Dr. Lenfant. Although the Institute can maintain research progress with the President's Budget funding level, there are numerous scientific opportunities that could be pursued if additional funds were available. High priority opportunities exist in each of the major program areas of the Institute. They are described in the following material.

Specialized Centers of Research (SCORs): Given additional funds, the Institute's first priority would be the restoration of reductions to its existing SCOR programs. These research centers provide a unique opportunity for basic and clinical scientists from a variety of disciplines to collaborate on research in a particular disease area. It should be remembered that the NHLBI is an Institute with a focus on specific clinical conditions, and a large measure of its success comes from the rapid translation of research findings to the bedside. The SCOR program is critical to that effort because it is uniquely and often exclusively the Institute's avenue for clinical research in a given disease area. The program ensures that advances in basic sciences are translated rapidly into clinical application and that clinical needs provide direction for the basic sciences. Over the years, work performed in the Institute's SCORs has contributed directly to the betterment of public health through improvements in the prevention, diagnosis, and treatment of disease. Recent research has produced enormous gains in our understanding of fundamental disease mechanisms that can rapidly be translated into new therapeutic interventions. The SCOR program is the NHLBI's best instrument for achieving that evolution.

The NHLBI has identified three new areas of scientific need for expansion of the SCOR program: Vascular Biology and Medicine, Sudden Cardiac Death, and Heart Failure. The FY 1991 cost of these new SCORs is estimated at $20 million.

Vascular disease, which cuts across the NHLBI programs in heart, lung, and blood disease, is important from the standpoint of its high incidence, serious morbidity, and significant mortality. Presently, no one clinical discipline is focused exclusively upon the diseases of the vasculature and, consequently, lessons learned by researchers in one of the related disciplines may be shared only within that discipline. New developments in the basic sciences, particularly in the fields of cell biology, molecular biology, and biochemistry, are bringing to light much knowledge about how cell behavior and communication affect the vasculature in health and disease. The SCOR in Vascular Biology and Medicine will provide an integrative environment for research to improve understanding of vascular disease and to develop and refine methods for its detection, management, and prevention.

Sudden cardiac death claims over 270,000 Americans annually and accounts for about 50 percent of all deaths from coronary artery disease. Yet, the mechanisms triggering the lethal arrhythmia remain obscure. Basic knowledge about electrical activity in cardiac tissue has been developed, but has yet to provide leads directly applicable to the clinical event. The Institute believes that the multidisciplinary, collaborative atmosphere of a new SCOR program will provide the impetus to translate basic electrophysiologic studies into clinically useful diagnostic and therapeutic approaches as well as foster the pursuit of new knowledge. Recent reports of an association between circadian rhythm and sudden cardiac death similar to that demonstrated for myocardial infarction provide clues to the pathophysiologic events precipitating a lethal arrhythmia. The new SCOR in Sudden Cardiac Death would pursue these research avenues.

The new SCOR in Heart Failure will address a condition that currently affects about 2.3 to 3.8 million Americans and is becoming an increasing problem as the population ages. For most patients with heart failure, therapy is palliative; the only treatment available for end-stage heart failure is a heart transplant. The NHLBI continues to pursue vigorously a number of therapeutic strategies, such as treatment with vasodilator drugs and the development of the artificial heart. Nonetheless, it is apparent that success in the clinical area depends on the existence of a parallel effort in basic research. At present, very little is known about the underlying mechanisms of heart failure. The relative roles of changes in gene expression, receptor regulation, ion channel and pump maintenance, and metabolic activity in myocardial dysfunction are poorly understood. Further, there are many unanswered questions about the mechanisms whereby cardiac myocyte necrosis occurs as a result of changes in structure and function of the heart and the coronary circulation. New knowledge of the pathophysiology, biochemistry, and molecular biology of heart failure will lead to improved strategies for the clinical care of patients with this condition.

National Marrow Donor Program (NMDP): The Institute has developed plans to expand the NMDP so that it may better meet the needs of the American people. The registry now lists nearly 100,000 potential donors, which had been the original goal, but it is now apparent that at least 250,000 donors are needed to provide a reasonable chance of matching any given patient with a donor. Further, there is a pressing need to include many more minority and international donors. Reaching the new goal of 250,000 will require that an additional 150,000 persons be typed for HLA A and B antigens, at an estimated cost of $11.5 million. Performing HLA-DR testing as well could be expected to double these costs.

The NHLBI also plans to expand its National Blood Resource Education Program to include public and professional education about bone marrow transplantation. Considerable media attention has been given to the plight of individual patients for whom donors are difficult to find, and a number of patient-focused, crisis donor recruitment drives have been undertaken. Measures need to be taken to ensure that prospective donors provide informed consent and meet certain requisite health criteria, and that samples are collected properly and efficiently. Given the prospects for expanded interest in bone marrow donation, an educational effort is essential to address these needs. The Institute estimates that $1 million could be used for this purpose.

Bone Marrow Transplantation and Gene Therapy: The NHLBI is planning a major expansion of its intramural gene therapy research program that is concordant with, and dependent upon, the parallel development of a clinical bone marrow transplantation (BMT) unit at the NIH Clinical Center. The estimated cost of the total program is $5 million in FY 1991.

The NHLBI intramural research program is engaged in a important effort to develop effective methods of genetic therapy for heritable human diseases within the Institute's mandate. Having successfully completed the world's first gene transfer experiment in humans, the program is embarking on new gene therapy protocols of historical significance. Currently under review is a protocol to treat adenosine deaminase (ADA) deficiency, a genetic disease that causes severe combined immune deficiency. This research is expected to have applicability not only to other bone marrow and genetic disorders, but also to revolutionary new treatments for cancer, viral disease, and cardiovascular disease. For example, the transfer and expression of the newly identified gene for cystic fibrosis in bronchial epithelial cells is being investigated. Use of gene therapy to treat such hemoglobin disorders as sickle cell anemia and severe Cooley's anemia is also under study. Gene therapy might also be used to alter cholesterol metabolism, thereby reducing the risk of heart disease in a wide patient population.

The possibility of treating genetic diseases through modifying the genome of somatic cells by gene insertion seems likely to be achieved in the next several years. It is probable that such experimental treatment will occur initially in the context of bone marrow transplantation (BMT). Accordingly, the NHLBI is planning to lead an intra-NIH effort to establish a clinical BMT unit in the NIH Clinical Center. The availability of a dedicated facility for BMT would enable intramural scientists to extend findings from their basic research laboratories and attempt innovative, experimental, therapeutic interventions for specific diseases. The BMT unit is needed to conduct investigations relative to the refinement and use of BMT therapy; more important, it is a critical resource that is needed to fully develop the overall gene therapy program. The presence of such a facility would assure the ability intramural scientists to assume a leading role in the development of this most promising area of research.

Before gene transfer can be considered as a therapeutic option in humans, substantial investigation will have to be performed in non-human primates to evaluate the efficacy and safety of gene transfer protocols. Various parameters that influence gene transfer into the hematopoietic stem cells of primates have been explored within the context of the Institute's existing primate bone marrow transplantation-gene transfer program. Although the results of the stem cell work are extremely encouraging, much additional work is required to increase the efficiency of gene transfer to a level that will be consonant with therapeutic applications. Consequently, the NHLBI is planning a major expansion of its primate gene transfer program.

The planned expansion will complement significant extramural research program designed and implemented by the Institute. For example, the NHLBI is supporting research to identify the location, function, and mode of action of genes that play a significant role in the pathogenesis of hypertension and to develop and use transgenic animals to study hypertension. If the genes contributing to the pathogenesis of hypertension can be identified and animal models of the disease process can be created, new therapeutic approaches may be developed.

Coronary Heart Disease (CHD) Prevention: Hypertension, which affects about 58 million Americans, is a major risk factor for the most commonly encountered forms of heart and blood vessel diseases. It accelerates the development of atherosclerosis of the coronary and peripheral arteries and is the single most important contributing factor to the development of stroke. During the past 20 years, many improvements have occurred in the control of hypertension. The public is more knowledgeable about hypertension, more likely to visit a physician for hypertension, and more likely to follow medical advice. During this same period, there has been a 57 percent decline in the national age-adjusted stroke mortality rate.

The overall health benefits associated with treating hypertension have been well documented. However, studies to determine whether treating mild-to-moderate hypertension reduces heart attacks and deaths from coronary heart disease have produced equivocal results, possibly because of the confounding influence of adverse effects of the drugs used in such studies. New classes of drugs have been increasingly recognized as possible approaches for initial treatment of mild hypertension, but there has not been a conclusive study of their comparative effectiveness. A recent report in the hypertension literature noted that "...large scale trials have not used newer antihypertensives such as calcium antagonists and angiotensin converting enzyme inhibitors. There are no comparable data for these widely used drugs, and we urgently need large scale comparative trials to assess the role of these agents as first line treatments in mild hypertension."

The NHLBI proposes to initiate a clinical trial to compare new antihypertensive medications with current therapy to determine whether the newer approaches are capable of achieving a reduction in the number of nonfatal heart attacks and the mortality from coronary heart disease. The total duration of the trial, including planning, intervention, follow-up of 7-9 years per patient, and data analysis, will be 12 years. Estimated first-year costs are $2.6 million; estimated total costs are $143 million.

Mechanisms of Bronchopulmonary Dysplasia: Bronchopulmonary dysplasia (BPD) is a chronic lung disease of infancy that affects about 8,000 babies born in the United States each year. Although mainly a consequence of neonatal respiratory distress syndrome (RDS), a complication of prematurity, BPD has also been reported in infants with pneumonia, meconium aspiration, cyanotic congenital heart disease, and apnea. The incidence of sudden infant death syndrome (SIDS) is about seven times higher in infants with BPD than in normal infants.

The NHLBI proposes to expand and diversify its program of basic research on BPD. The recent development of new cellular and subcellular approaches for investigation of pathogenetic mechanisms has created opportunities for morphologic, physiologic, cellular and molecular level studies of BPD. Detailed studies are needed of pulmonary function as it relates to lung morphology and biochemistry during lung injury, recovery, and growth in subjects at various stages of disease. A need also exists to develop cytological, biochemical, and molecular information on cellular events associated with lung development and with lung injury in premature newborns during the first few weeks of postnatal life.

The Institute will also encourage studies of neuroendocrine cell function, growth factor expression, receptors, and collagen production, including that of basement membranes and their role in the repair process under both normal circumstances and conditions of widespread scarring. Studies directed at understanding protease/antiprotease balance, inflammatory mediators, and cells of the immune response are also needed, as well as research to identify the cell populations involved in the regeneration of badly damaged lungs. This research will shed light on the natural history of BPD and on the pathophysiology of BPD in comparison with normal lung development. The findings will add considerably to our knowledge of how to prevent and treat BPD, and may be expected to lead to a greater understanding of lung injury and repair in other conditions as well. The estimated cost of this expanded program is $2 million in FY 1991.

Prevention and Treatment of Asthma in Children: Asthma is a serious chronic disease affecting approximately 10 million people in the United States, 3 million of whom are under the age of 18. Costs from asthma care exceed $4 billion per year. Asthma is probably the only treatable condition whose prevalence and severity is increasing, attesting to the need at the national level for asthma education and more effective treatment of this disease.

Since the mid-1970s, behavioral research has addressed ways of teaching asthmatics and their families to manage the disease. Asthma education programs have resulted in fewer attacks, better adherence to medication, fewer days lost from school, fewer visits to the emergency room, and improved school grades. These findings have been disseminated widely. The National Asthma Education Program (NAEP), initiated by the NHLBI in 1989, is expanding these efforts.

Because of recent evidence suggesting that childhood asthma predisposes one to subsequent development of chronic obstructive pulmonary disease (COPD), and that the course of COPD is most severe in patients with low initial lung function levels, the NHLBI proposes to initiate a clinical trial to examine the effects of a structured, stepped-care drug intervention program in maximizing and maintaining optimal lung function in children and reducing the risk of lung disease in later life. If our hypothesis proves correct, this program should greatly benefit children who would otherwise grow up with an increased risk of lung disease, and the high medical costs and suffering that go with it. The estimated first year cost of this clinical trial is $1 million, and total costs are $40 million over nine years.

National Heart Attack Alert Program: Coronary heart disease (CHD), the leading cause of death in the United States in both men and women, caused 511,000 deaths in 1988. People with CHD often do not reach appropriate medical care, and those who do often do not reach it in time for the latest life-saving technologies to be effective. Minimizing the amage resulting from a heart attack by preserving cardiac tissue is of paramount importance.

The Institute has been considering the establishment of a national education program to alert health professionals, their patients, and the public about the need to respond with immediate action at the first signs or symptoms of a heart attack. Recent scientific advances and especially the development of thrombolytic therapies have provided effective methods for reducing the morbidity and mortality associated with CHD. Yet available data suggest that only a small percent of the heart attack patients eligible for thrombolytic therapy actually receive it.

In September 1989, the Institute convened a small workshop of leading experts in cardiology, emergency medicine, and behavioral medicine to assess the advisability and feasibility of creating an education program to emphasize the need for early heart attack intervention. The NHLBI was advised to proceed with due caution in developing the program. The workshop recommendations were sufficiently thought-provoking to prompt the Institute to consider the issues in more detail.

The Institute will sponsor a forum entitled "Rapid Identification and Treatment of Acute Myocardial Infarction: Issues and Answers" in October 1990. Key issues will be introduced by recognized experts and discussed by forum participants who will then formulate their recommendations. Proceedings of the forum will be prepared and disseminated throughout the scientific community to increase awareness of the issues and to secure a broad range of comments concerning the proposed educational effort. The proceedings will also be used by Institute staff to weigh the advisability of establishing a program and to determine how such a program should be structured.

AIDS: New research opportunities in the Institute's AIDS program are related to the safety of blood transfused to HIV infected neonates, and to the cardiac and pulmonary complications of AIDS in infants and children.

Cytomegalovirus (CMV) is the most common cause of serious viral infection in all AIDS patients and involves many organs. Transfusion-transmitted CMV infection is fairly common and is particularly important in infants who do not have antibody against the virus. Substantial numbers of HIV infected individuals are transfused during the course of their disease and it is usually the most immunosuppressed patients who require transfusion. Currently, blood is not tested for CMV before it is administered to patients. Although the effects of removing most of the white cells from transfused blood probably would decrease the incidence of CMV infection, this method of preparation of blood components has not been tested in this population. The Institute, as part of its pediactric AIDS research efforts, proposes to study the effects of transfusion of blood negative for CMV, as well as blood that is depleted of white cells to determine if it decreases the incidence of serious CMV infection in HIV infected neonates. This study will begin to provide the information we need on this subject.

Infants and children constitute one of the most rapidly growing groups of infected individuals in this country. Pneumocystis carinii pneumonias, as well as lymphoid interstitial pneumonia, are major problems affecting infants and children infected with HIV. A group of studies, initially funded in FY 1989, will support investigation of the factors that lead to the development of these disorders, and will help determine their optimal treatment. We propose to supplement these projects to support the development of blood tests and other analytic procedures that can be used to facilitate early diagnosis of these disorders and to assess their response to therapy.

LOST OPPORTUNITIES

Mr. Early. Will any significant new research initiatives or opportunities be lost or delayed by lack of funds in the FY 1991 budget?

Dr. Lenfant. There are several new research initiatives and opportunities that cannot be supported with the funds available in the President's Budget.

Mr. Early. Please provide, for the record, a list of these along with a brief description and the funding requirements associated with each.

Dr. Lenfant. I have already mentioned the opportunity for new research centers, new clinical trials, new education programs, and the exciting new opportunities in gene therapy and bone marrow transplantation. In addition to these, I have deferred several initiatives until the funding picture is clarified.

Title	First Year Cost	Total Cost
HIV Immunoglobulin Production for Study of HIV-IG in Infants Infected with HIV	$150,000	$150,000
Behavioral Stressors and Lipoprotein Metabolism	1,365,000	7,396,000
Cardiovascular Disease Nutrition Education for Adults with Low Literacy Skills	1,000,000	6,000,000
Cardiovascular Device-Centered Infections	1,200,000	6,498,000
Cell Biology of the Endocardial Endothelium	500,000	2,708,000
Molecular and Genetic Mechanisms Controlling the Metabolic and Oxidative Potential of Heart Muscle	1,200,000	6,500,000
Feasibility Study of First Line Drug Selection in the Treatment of Hypertension	500,000	500,000
Smoking Cessation and Relapse Prevention Strategies for Lower SES Groups	1,625,000	8,802,000
Contractile Protein Function in Pulmonary Smooth Muscle	1,100,000	5,958,000

PROFESSIONAL JUDGMENT BUDGET

Mr. Early. Doctor, does your institute prepare a professional judgment budget?

Dr. Lenfant. Yes, the Institute prepares a professional judgment budget as part of the preliminary budget process.

Mr. Early. Would you tell us what the bottom line is for this budget.

Dr. Lenfant. The preliminary budget request for NHLBI was $1,482,473,000.

Mr. Early. What are the differences between your professional judgment budget and the request before us?

Dr. Lenfant. The FY 1991 President's Budget proposes a 3.7 percent increase over FY 1990 for the NHLBI. This increase is intended to provide more emphasis on basic research, and therefore most of the increase is allocated towards research project grants and intramural research. Other mechanisms remain the same or increase a small amount because they are AIDS-related research or minority programs that have received special attention.

The professional judgment budget included additional funds which would permit the Institute to pursue new research opportunities and expand existing programs as follows.

In research project grants, the Institute would restore negotiated reductions and support noncompeting and competing grants at their approved or committed levels. Funds were included for additional new and competing renewal awards to enable the Institute to support approximately 35 percent of approved applications.

The budget policy for centers in the FY 1991 request is to keep them at their FY 1990 level, approximately 24.3 percent below recommended levels. The centers programs are crucial to the effort to rapidly translate recent research finding to the bedside. At the professional judgment level the Institute would restore these reductions and provide increases in funding to augment existing centers and begin new center programs. A new Specialized Center of Research in Vascular Biology would help develop a comprehensive knowledge of the mechanisms involved in maintaining normal vascular structure and function and in the pathophysiology of vascular disease.

A new center program is sudden cardiac death would pursue promising new research avenues on the events which precipitate letha arrythmias. New heart failure centers would support the basic and clinical research that must parallel the research on existing therapeutic strategies for the failing heart.

In other research, NHLBI demonstration and education programs offer an effective mechanism for demonstrating and disseminating the benefits of research results to the public. The Institute proposed to expand this research program in the areas of: effective management strategies for educating asthmatic children and their parents; intervention strategies for risk factor reduction at the work site; and dietary intervention strategies for reducing cardiovascular mortality. Additional funds were also provided for minority biomedical research support awards and for research career awards such as the academic award in systemic and pulmonary vascular disease.

The NHLBI is interested in insuring that research training in the new techniques of molecular and cellular biology is available to individuals interested in heart, lung and blood diseases, and blood resources. The professional judgment level would support new awards in this area. In addition, the Institute would implement new training programs in such areas as clinical trial design and methodology, biostatistics, epidemiology and population demography.

In research and development contracts, funds were included to provide additional support for the National Bone Marrow Donor Program, and to conduct major high priority clinical trials which are likely to have a significant impact on public health.

The professional judgment budget included an additional 39 full-time-equivalent positions for the intramural research program. This increase, together with additional funds, would permit the Institute to pursue expanded gene transfer technology, bone marrow transplantation, and cystic fibrosis research and full development of the newly created Laboratory of Cardiac Energetics.

Additional funds were provided in research management and support to expand the activities of the NHLBI education programs in risk factor reduction, including the new National Heart Attack Alert Program to help physicians educate their patients about signs and symptoms of heart attack.

Funding was provided in construction for upgraded research facilities and sophisticated research instrumentation required to implement new research technology in the area of molecular biology and for state-of-the-art magnetic resonance imaging in the area of cardiac energetics, gene replacement therapy, pulmonary complications of AIDS, and bone marrow transplantation.

CYSTIC FIBROSIS

Mr. Early. Two years ago, the NHLBI, along with NIDDK, initiated some Cystic Fibrosis Research Centers in collaboration with the CF Foundation. A lot of progress has been made, and this past year a breakthrough occurred -- the defective gene has been located. Now we are moving quickly to find a treatment, if not a preventive procedure. Doctor, will NHLBI and NIDDK continue to strongly support these centers for FY 1991?

Dr. Lenfant. The NHLBI is committed to providing continued support for three Specialized Centers of Research in Cystic Fibrosis which were initiated in FY 1988 to meet the challenge of understanding and conquering this debilitating disease. These five-year grant programs will continue through FY 1992 at the University of North Carolina, the University of Iowa and the University of California at San Francisco. We do not know how many will be renewed at that time.

Mr. Early. Tell us a little more about the progress your Institute is making in cystic fibrosis research.

Dr. Lenfant. A number of significant scientific advances have been made in cystic fibrosis research supported by the Institute. A well-known hallmark of cystic fibrosis is the excessive mucus that plugs the airways, making breathing difficult and leading to the infections that plague those who suffer from this genetic disease. Research investigators have characterized the biologic defect as an abnormal regulation of channels controlling the movement of ions (namely, chloride and sodium) through the cell membrane, contributing to the abnormally dehydrated respiratory tract fluid and impaired clearance of mucus in the airways. Investigators supported by the Institute have recently identified another important enzyme, protein kinase, that regulates the chloride channel in airway cells whose regulation is aberrant in this disease. This finding provides further evidence that cystic fibrosis is a membrane disorder. Progress has been made _in vitro_ model systems through development of immortalized normal and airway epithelial cells. These cells provide a vital resource for biochemical/molecular analyses aimed at delineating the basic mechanisms underlying cystic fibrosis, as well as serve as _in vitro_ models for development of new therapies. Progress has also been made in treatment. Building on the observation of excessive sodium absorption by the airway epithelia in patients, a small clinical trial was undertaken to evaluate the effectiveness of a sodium channel blocker, amiloride, in the treatment of lung disease; promising results have shown that aerosolized amiloride slows the progression of the lung disease which is so damaging in these patients. If confirmed in a larger clinical trial, these findings would represent a major advance in therapy for cystic fibrosis.

DEEP VENOUS THROMBOSIS

Mr. Early. I hear that deep vein thrombosis is a very important public health problem. What research are you doing about this condition?

Dr. Lenfant. Deep venous thrombosis (DVT) is a disorder of high frequency with significant risks for serious complications including death. Symptoms and signs of DVT may be absent or non-specific and the first sign may be the development of a life-threatening pulmonary embolus. Objective tests have been developed to improve the diagnostic accuracy and the Institute currently supports a program on improved instrumentation for the diagnosis of venous thrombosis. Five grants are in their fourth year of a five year project period so it is too early to report results.

Research supported by the Institute includes studies of the natural inhibitor systems against clot formation, improved approaches to prevent thrombosis using anticoagulants such as heparin and recombinant hirudin, the development of improved agents to enhance the lysis of clots and prospective clinical trial studies in the prevention of DVT in surgical patients.

Mr. Early. Can this condition be prevented?

Dr. Lenfant. Yes, it can. An important conclusion in the report of an NIH Consensus Development Conference supported by the NHLBI in 1986 was that DVT and pulmonary embolism in high-risk patients can be significantly reduced by prophylactic regimens, and needed to be employed more extensively. Effective preventive regimens differ and should be determined with consideration of the patient's disease and degree of risk. The cost-effectiveness of preventive measures has been demonstrated.

RESEARCH CAREER AWARDS PROGRAM

Mr. Early. Doctor, would you bring us up to date on your Research Career Awards Program?

Dr. Lenfant. The Institute's research career development program continues to facilitate the establishment of research careers among promising investigators in the areas of heart, lung, and blood research and to enhance the development of selected subject areas in medical school curriculum. In FY 1989, the Institute made 391 research career program awards, for a total of $25,564,000. Research career programs designed to provide research experience for promising investigators include: the Research Career Development Award, the Clinical Investigator Award, the Physician Scientist Award, and the Minority Faculty Development Award. Academic award programs designed to encourage developments in medical school curriculum include the Preventive Cardiology Academic Award, the Preventive Pulmonary Academic Award, and the Transfusion Medicine Academic Award. The annual announcements of each of these programs now place special emphasis on increasing the opportunities for minority participation. Two of the three current academic award programs will be announced for the final time in FY 1991: the Transfusion Medicine Academic Award (in its ninth competition in FY 1991) and the Preventive Cardiology Academic Award (in its 13th competition in FY 1991).

Mr. Early. Are you planning any new initiatives in this area?

Dr. Lenfant. In FY 1991, the Institute will initiate an Academic Award in Systemic and Pulmonary Vascular Disease. The primary objective of this initiative is to encourage the development and/or strengthening of clinical, educational, and research programs in vascular medicine in schools of medicine and osteopathy. The program will serve to enhance and coordinate diagnostic and therapeutic skills in the clinical management of patients with vascular diseases such as atherosclerosis, lipid metabolic disorders, hypertension, thrombosis, and vasculitis. Schools of medicine or osteopathy in the United States will be eligible to compete for nonrenewable awards for project periods of up to five years.

Mr. Early. How do you plan to fund this initiative, since no increase is proposed for Research Career Awards in the FY 1991 budget request?

Dr. Lenfant. In FY 1991, the Institute plans to fund up to five awards under the new initiative, at a cost of $750,000. Over its nine-year anticipated lifespan, the initiative may result in awards to as many as 25 institutions and may cost a total of $20 million. By reducing funds available for other career awards, the Institute will be able to fund the new academic award with no increase in the overall budget.

CONSTRUCTION GRANTS

Mr. Early. Doctor, the budget request does not include funds for extramural construction. Is this an area that needs to be addressed?

Dr. Lenfant. Yes, the construction of new or the improvement of existing biomedical research facilities in the extramural community is essential to address a variety of unmet needs. If construction grants were provided, the heart, lung, and blood research programs would be enhanced in a number of areas.

Construction of facilities would allow a broadening of the science base by establishing facilities for research programs at the cutting edge, for example, molecular biology. These awards would also permit institutions to deal with physical deterioration through normal use and aging, and to meet new regulatory standards affecting animal care, laboratory practice, and health, safety, and environmental issues. While the NIH has chosen to apply the available resources to other higher priority areas, we believe that the productivity of our research programs would be greatly enhanced if the research facilities were improved.

CARDIAC SURGERY UNIT

Mr. Dwyer. Dr. Lenfant, a number of my constituents have contacted me to protest the Institute's plans to close its cardiac surgery unit. What alternative facilities has the NHLBI approached to become contractees for cardiac surgery?

Dr. Lenfant. The NHLBI is initiating an open competition to award one or more contracts with local hospitals to carry out cardiac surgery in support of and in collaboration with our cardiology program. It is expected that the award(s) will be made in September 1990. In the interim, NHLBI has in place emergency contracts with the three most active hospitals in the local area doing cardiac surgery: Washington Hospital Center, Georgetown University, and Fairfax Hospital. To date, more than a dozen patients have successfully received cardiac surgery under this arrangement.

Mr. Dwyer. What will happen to those individuals, formerly treated at NHLBI, who need additional surgery?

Dr. Lenfant. The Institute has an ongoing commitment to its patients, past and present. The new program is already in place and more than a dozen patients have successfully undergone surgery at one of three local hospitals which are providing these services for us. All costs not covered by the patient's insurance will be underwritten by the Institute; there will continue to be no cost to the patient.

We will continue to evaluate potential surgery patients in the cardiology program, and will provide medical treatment at the Clinical Center. We will also continue the outpatient clinic for patients who have previously had cardiac surgery at the Clinical Center. Former and new patients needing surgery will be referred to one of the local surgery facilities. A close working relationship between the clinical and research staff of our Cardiology Branch and the surgeons at the local hospital will ensure consistent care of the highest quality. Each patient has been sent a letter from the Institute informing them of how these services will be provided.

Mr. Dwyer. Besides benefitting the patients, the cardiac surgery unit at NHLBI was of enormous benefit to cardiac surgeons wishing to learn new techniques, etc. How will NHLBI continue to provide leadership and expertise to young cardiac surgeons in this area?

Dr. Lenfant. The cardiac surgery unit has had a long tradition of preparing young surgeons-in-training for productive academic careers. This training has been accomplished primarily through the Clinical Associate in Surgery Program. Each year, four associates were appointed for terms of two years. The associates spent nine months assisting in cardiac surgery and cardiology and the remainder of the two years in laboratory research. The unique feature of the program has been the extended experience in laboratory research, an experience not generally available elsewhere. Much of this research, especially in recent years has not involved surgery.

We continue to believe that the NHLBI has an important role in the development of young investigators for academic careers in cardiac surgery. Our principal role in this educational process is to train the future academic surgeon in the methodology of scientific research and provide exposure to the most exciting areas of biomedical science that will affect his discipline.

To accomplish these goals, we have initiated a new Surgical Associate Program, to begin July 1991. Applicants will be limited as before to individuals who have completed at least two years in an approved surgery residence program and are training for an academic career in cardiothoracic surgery. Up to four Surgical Associates (each year) will have the opportunity to spend two years of full-time research in any of the laboratories or branches in the NHLBI intramural program. We are confident that this rich research experience will contribute importantly to the training of young cardiac surgeons.

In addition to our intramural program, the NHLBI will continue to support advances in cardiac surgery through the awarding of training grants to top research and teaching institutions.

ASTHMA EDUCATION PROGRAM

Mr. Hoyer. What is the status of the National Asthma Education Program?

Dr. Lenfant. The National Asthma Education Program (NAEP) was launched in March 1989. The primary goal of the program is to improve awareness of asthma as a serious chronic disease and to set in motion a host of activities and programs to improve attitudes, practices and behavior of patients/public and health professionals related to management and control of asthma in this country. A national coordinating committee of professional, voluntary, government and lay organizations forms the core of the program. Presently, 27 organizations with interest in improving asthma care make up the NAEP Coordinating Committee. The committee has met twice and has identified key areas of concern for the program. To best address the issues facing the program, the NAEP agreed to establish panels and subcommittees to help set direction in specific areas.

The first major task of the NAEP was to develop a report on Management of Asthma to provide guidelines for health professionals on diagnosis and treatment issues. The report will also include information on the roles of exercise and allergy in asthma, and asthma in special populations such as the elderly and pregnant women. The report will be discussed at the next coordinating committee meeting in June 1990. It is planned to be completed in December 1990 and will be distributed widely to primary care physicians in a "Physician's Kit" which will also contain booklets on Teaching Your Patients About Asthma (for health professionals), and Managing Your Asthma (for asthma patients). In addition, the NAEP has created three subcommittees: Professional Education, School Asthma Education, and Patient/Public Education. Each subcommittee will develop activities and programs targeting these major areas. Educational materials for asthma patients, their families and health professionals are also planned. Since over one-third of the people with asthma are children, the Institute is working with the Department of Education to explore collaborative efforts to develop asthma education activities and programs for the schools which target teachers, nurses, coaches and school administrators. The potential outcome would be reduced absenteeism, better recognition that asthma is a serious disease that requires proper management, and increased participation in school activities by children with asthma. The NHLBI is confident that these coordinated efforts will make a major impact on both morbidity and mortality of asthma in children and adults in the United States.

Mr. Hoyer. How much is the Institute spending on the program in FY 1990 and FY 1991 under the President's request?

Dr. Lenfant. The Institute looks at the total amount available for all its education programs rather than focusing on a budget for the individual education programs. At present, the Institute divides the amount available for education programs into two funding pools. One pool of funding is allocated so that a specific sum of money is identified with each of our several education programs. The second pool of funds supports several or all of the education programs. Included in this pool are crossover initiatives such as multiple risk factor education efforts, initiatives implemented at the worksite, and initiatives that target special populations such as those directed toward a specific minority group. Staff salaries and related support costs are also included in this second pool. It is not possible to attribute accurately the costs in this pool to a specific education program.

Costs that are specifically identifiable with the National Asthma Education Program are $488,000 in FY 1990 and $475,000 in FY 1991. The overall budget for the Institute's education activities, including the National Cholesterol Education Program, National High Blood Pressure Education Program, NHLBI Smoking Education Program, National Asthma Education Program, National Blood Resources Education Program, and National Heart Attack Alert Program is $5,736,000 in FY 1990 and $6,056,000 in FY 1991.

Mr. Hoyer. How does the asthma education program compare to the other major programs under the institute's jurisdiction in terms of size and scope and plans for growth?

Dr. Lenfant. The National Asthma Education Program (NAEP) is the youngest of the national education programs of the National Heart, Lung, and Blood Institute (NHLBI). It is slightly over a year old. Even though the program is in its early stage of development, it has vigorously taken on the challenges of identifying key areas of concern to the asthma community and has already initiated a number of plans to achieve its goals and objectives. In comparison to the other major programs when they were at this stage of development, the NAEP's plans are as dynamic and challenging.

The NAEP sees many special areas of need and many target groups that need to be reached. As prevalence of asthma and morbidity/mortality increase as well as the number and rate of hospitalizations and school absentees, there will be increased effort by the program to implement activities and programs to reverse these trends. The growth of the program, however, will be contingent upon competing demands for resources. Future plans for growth will be commensurate with available resources.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Mr. Hoyer. What do we know about the reasons for chronic obstructive pulmonary and associated diseases and why they are rising faster than any of the five highest causes of death?

Dr. Lenfant. Chronic obstructive pulmonary disease is a slowly developing, irreversible and generally progressive group of separate but often interconnected disease processes which includes emphysema, chronic bronchitis and asthmatic bronchitis. This group of associated coexisting diseases represents the fifth leading cause of death, accounting for approximately 80,000 deaths in the United States in 1987. A variety of factors have been implicated in the development of chronic obstructive pulmonary disease, including cigarette smoking, air pollution, history of childhood respiratory problems, chest infections, occupation, and hereditary factors. However, cigarette smoking is now recognized as the major risk factor and the predominant cause of this debilitating condition. Respiratory symptoms and lung function abnormalities increase shortly after the onset of smoking and are much greater in heavy smokers than light smokers. The risk of death is directly linked to the number of cigarettes smoked daily and the number of years the individual has maintained the smoking habit.

In the last several years there has been a relatively sharp rise in mortality from chronic obstructive pulmonary disease, particularly in men. Since this is a slowly developing disease, it is likely that much of the current mortality can be directly attributed to the harmful effects of cigarette smoking among men who began smoking some 25-30 years ago. Because of the difference in the onset of cigarette smoking, the trend in mortality in women has lagged behind men, but rates in women are expected to increase in future years with the significant increase in smoking rates in this segment of the population.

As a result of the heightened awareness of the health hazards of cigarette smoking, there has been an overall decline in smoking rates in the United States. However, despite this recent decline, a significant proportion of the population continues to smoke. As an alternative approach to address this problem, the Institute sponsors a multi-center clinical investigation, the Lung Health Study, to identify men and women with early signs and symptoms of chronic obstructive pulmonary disease and to determine whether smoking cessation programs and/or bronchodilator therapy can influence the course of disease before the onset of clinical illness. Approximately 6,000 smokers, aged 35-59 with evidence of airways obstruction have been recruited into the study by ten clinical centers. All subjects will be followed at yearly intervals for five years using a common protocol. This is the first large scale population-based pulmonary study to examine whether modification of risk factors can alter the course of the disease. If this approach is successful, there may be justification for identifying early airways obstruction in smokers and concentrating intervention resources on this group.

CARDIOVASCULAR DISEASE AND MINORITIES

Mr. Hoyer. Stroke in black Americans in 1987 was twice as common as among the general population. Blacks are three times more likely to die because of problems associated with hypertension. What are some of the behavioral and physiological differences that may account for these statistics?

Dr. Lenfant. Recognizing that essential hypertension is a major health problem among black Americans, the Institute initiated a program of research in 1983 to investigate the biological and behavioral factors that may affect hypertension in blacks. Findings from these studies suggest that race differences in hypertension may result from a combination of physiological, environmental and behavioral factors. For example, stress produces smaller increases in heart rate and larger resistance in blood vessels in blacks than in whites, and there are known race differences in sodium metabolism, plasma renin activity and behavior.

Race differences in smoking behavior may also account for some portion of the race differences in hypertension. Data demonstrate that in spite of dramatic decreases in the rate of smoking among adults in general in the United States over the past 20 years, comparable decreases have not been realized for minority groups. Blacks continue to smoke at a higher rate and are less successful at maintaining smoking cessation than are whites.

Race differences in the pattern of coronary heart disease (CHD) between black and white Americans may reflect differences in the social and individual characteristics of these groups in seeking and obtaining care for CHD prior to an event. For example, differences between blacks and whites in recognition of and attention to CHD symptoms, access to and prompt use of medical care, and referral to and use of diagnostic and therapeutic options may contribute to the striking differences in the higher mortality rate associated with hypertension among blacks than among whites.

Race differences in obesity may contribute to the race differences in hypertension. Obesity is regarded as a significant predictor of CHD and is positively associated with elevated blood pressure, as well as diabetes and very low density lipoprotein. A higher rate of obesity in black women, often developing in adolescence, may contribute to the higher rate of hypertension and of CHD mortality for black as compared to white women.

Although we do not know all of the reasons why death rates from cardiovascular diseases are higher among blacks than whites, the Institute decided to begin a new initiative that should help reduce deaths from stroke. This year, the Institute will begin a special initiative on stroke that will focus on 11 southeastern states, known as the "Stroke Belt," in which stroke mortality rates are higher than in the rest of the country. The Stroke Belt initiative will continue to emphasize the very effective role of churches as an avenue to increase public awareness on the need for high blood pressure control and smoking cessation to decrease the risk of stroke. In addition, a mass media effort includes a plant to have a state health department representative in each stroke belt state work with radio and television stations on a "Strike Out Stroke" campaign. Finally, state health departments located in stroke belt states will receive funds to initiate projects that assess high risk target audience needs and identify opportunities for more effective delivery of medical and/or educational services.

Mr. Hoyer. Do you have any pending or outstanding requests for applications on studying these problems?

Dr. Lenfant. The Institute currently has several programs of research designed to address race differences in hypertension and CHD-related morbidity and mortality. In 1987, we began a program on Health Care-Seeking Experience Among Blacks for CHD which investigates the experiences of minority individuals between the earliest symptom and appropriate medical care. It gives special attention to research on individual and environmental factors that might influence the health care-seeking experiences of blacks. In 1989, we began a program on Smoking Cessation Strategies for Minorities in which investigators are developing and testing smoking cessation techniques designed specifically for urban and rural blacks, Hispanics, and Native Americans. In the Health and Growth Study program, investigators are studying the predictors of the transition to the obese state for black and white adolescents, as well as factors associated with this transition and how these factors relate to other CHD risk behaviors. Additionally, several investigators continue to explore directly the biological and behavioral factors that may explain race differences in hypertension. Finally, the Institute is currently developing a request for applications entitled "Mechanisms and Pathogenesis of Hypertension in Blacks."

WOMEN AND HEART DISEASE

Mr. Pursell. Heart disease is a major killer among American males, and is responsible for thousands of premature deaths annually. Hundreds, probably thousands, of studies have been conducted to determine how to reduce this rate. Have any of these studies focused on the rate of heart disease among women?

Dr. Lenfant. A number of studies have examined the rate of heart disease among women. As with men, we know that heart disease is the leading cause of death among women in the United States. In fact, from the age of approximately 55 years and on, heart disease is the number one cause of death in women. In 1986, virtually the same number of women as men died of heart disease (nearly 400,000 men and over 350,000 women), but the rates differ because of the greater numbers of women who survive past age 65. Thus, a large amount of data exists which underscores the fact that heart disease is not only a disease of men, but a serious health problem for women, as well.

Although we have a great deal of information concerning the rates of heart disease in both women and men, we have less information concerning the causes of heart disease in women and the relative importance of certain risk factors. We also lack information on reasons underlying the differences in heart disease rates between men and women. Further research is needed to better understand the disease process in women and to understand gender differences in heart diseases.

A number of researchers believe the increased rates of heart disease in older women are in association with the menopause and the subsequent reduction of HDL-cholesterol levels attributable to decreasing estrogen production. Women who receive estrogen replacement maintain HDL-cholesterol levels similar to their premenopausal years. In many studies women who have used estrogen replacement therapy have substantially lower rates of heart disease and heart disease mortality than women who have not received replacement therapy. Much of this data, however, is derived from women who received estrogen replacement therapy in the mid-1970's or earlier, when the estrogen dose tended to be about twice (or more) the amount currently used. Additionally, during that time period, progestational agents were not often used in conjunction with estrogen replacement. Because more information is needed, the Institute has sponsored a clinical trial called Postmenopausal Estrogen/Progestin Interventions (PEPI). This trial addresses some of the significant issues concerning the role of estrogen replacement therapy in reducing heart disease mortality among women.

Mr. Pursell. Do you think women in America are fully aware of the dangers of heart disease in women, and do you believe women have the resources available to practice good preventive medicine?

Dr. Lenfant. Recent studies have highlighted the need for better information on risk factors for heart disease in women. Research on gender differences indicate that men have higher rates of heart disease across all ages, but women with heart disease suffer more severe sequalae and have higher mortality rates following myocardial infarction.

For a number of years the Institute has conducted educational programs to inform both men and women about the risk factors associated with heart disease, and ways in which heart disease can be prevented. In particular, a workshop on Coronary Heart Disease in Women was convened in January, 1986, and a Seminar Series for Women is planned for the Fall 1990. In addition, a working conference on Cholesterol and Heart Disease in Older Persons and in Women will be held June 18-19, 1990. However, we still have much to learn about the importance of various heart disease risk factors for women, and especially about why women have lower rates than men. More research is needed in this area so that preventive efforts can be enhanced for women.

HEALTHY DIET FOR YOUNG AMERICAN MALES

Mr. Pursell. For years, researchers have known that if the American male maintains a sensible diet, he can greatly reduce the chances of heart disease. Is the National Heart Institute, CDC, American Heart Association and others emphasizing this for young males as well?

Dr. Lenfant. Recently the National Cholesterol Education Program's (NCEP) Population Panel made dietary recommendations for all healthy Americans, two years of age or older. The Report and Recommendations were unanimously endorsed by the NCEP Coordinating Committee, including the liaison members, e.g., the Centers for Disease Control (CDC) and the American Heart Association. The population approach involves a number of strategies including the teaching of nutrition in the schools, modification of food offerings in school cafeterias (school lunch program), better labelling of food contents and the development and provision of food snacks for children and adolescents that contain less fat, especially saturated fat. We believe that the concepts can be effectively emphasized in young males because of the significant risk of coronary heart disease (CHD) at an earlier age in men and because of the known benefit of reducing the risk of CHD through lowering elevated blood cholesterol. The NCEP recommendations, would reduce blood cholesterol levels in the general population, through dietary change to reduce total fat to about 30 percent of calories, saturated fatty acids to less than 10 percent of calories and cholesterol intake to less than 300 mg per day.

HEMOPHILIACS AND AIDS

Mr. Porter. AIDS has had a devastating effect on thousands of people in this country. Perhaps the most tragic impact has been on the hemophiliac population which is so dependent on the nation's blood supply. What effect have the HIV virus and AIDS had on the hemophiliac population in this country?

Dr. Lenfant. The impact of AIDS in patients suffering from hemophilia has been truly devastating. Over 1000 patients have contracted AIDS, and a significant number have already died. Furthermore, 75-85 percent of adult hemophilia patients in this country who receive coagulation factor concentrates and approximately 50-55 percent of pediatric hemophilia patients test positive for antibody to HIV.

Mr. Porter. Do hemophiliacs derive the same benefit from AZT treatment as the general population?

Dr. Lenfant. Patients with hemophilia clearly derive the same benefits from AZT treatment as other treatment groups. Approximately 50 percent of HIV-infected hemophilia patients in the U.S. are receiving AZT treatment. Patients are generally placed on AZT therapy when the concentration of immune helper cells decline to a certain level.

Mr. Porter. Is there any chance of reducing or eradicating the HIV virus from the hemophilia population?

Dr. Lenfant. The recent application of heat and chemical viral inactivation procedures to the manufacture of clotting factor concentrates has virtually eliminated the transmission of HIV and other transfusion-transmitted viruses to hemophilia patients. Consequently, those patients not infected with HIV will benefit greatly from the newer products. Major research efforts are currently focusing on the development of antiviral therapeutics to block and eliminate HIV in patients already infected with the virus.

Mr. Porter. What should Congress be doing to ease this burden on the hemophilia population?

Dr. Lenfant. It is essential that Congress continue to provide resources for research on this devastating disorder. Congress should also facilitate the rapid introduction of the newer coagulation products including those developed by genetic engineering techniques.

NATIONAL MARROW DONOR PROGRAM

Mr. Young. Dr. Lenfant, As you know the National Marrow Donor Program is saving lives every day, with 25 to 30 unrelated transplants being performed each month. The Committee in 1988 directed that the Registry be transferred from the Navy to your Institute and for the past 1 1/2 years you have been overseeing its operation. How do you view the accomplishments of the national registry and where do we go from here?

Dr. Lenfant. We view the accomplishments of the National Marrow Donor Program (NMDP) very positively. The size of the registry has tripled and the number of transplants done each month has doubled. The program is implementing new strategies for recruiting marrow donors: 1) a pilot program developed in one center to approach whole blood donors as marrow donors has been expanded to five additional blood centers; 2) the relationship between the NMDP and LIFE-SAVERS Foundation (LSF) has grown as the LSF has responded to patient-focussed crisis-related donor recruitment drives by helping to organize and raise funds to defray the cost of HLA typing resulting from such drives; LSF and other groups have begun community-oriented recruiting for donors. The program is beginning to develop materials from the repository of donor-recipient cell pairs for research in HLA typing and matching as well as for use in the upcoming International Workshop on Histocompatibility Testing. Finally, research needed to enhance bone marrow transplantations as a viable treatment modality for a variety of diseases is beginning to be expanded.

Mr. Young. Dr. Lenfant, As you have said the national registry is working and saving lives. We now have more than 90,000 volunteers who have been typed to be listed in the registry and we are well on our way to a goal of 250,000 volunteers here and 1 million worldwide. Until we reach these goals, however, finding a matched donor for every one in need of a transplant remains a large problem. How can we solve this problem, especially with regard to lack of volunteers within a number of ethnic groups?

Dr. Lenfant. The National Blood Resources Education Program (NBREP) of the NHLBI is developing a strategy of market research, targeted media drives, and work with community groups to supplement similar activities of the National Marrow Donor Program (NMDP) and its individual patient-oriented donor recruiting activities. The Institute will use techniques that have been successful in dealing with diseases, which affect minorities disproportionately, such as hypertension in black Americans. The NHLBI is also interested in research utilizing better and more precise techniques for HLA typing, of particular importance since the standard serological reagents are less reliable in minorities.

It is important, however, to recognize that the goal of 250,000 potential donors must be regarded as preliminary and subject to change as we gain knowledge about the frequency of various HLA type combinations in different population groups. Furthermore, even with a registry of several million, it will not be possible to find a match for every patient. Some will have HLA combinations that are just too rare.

Mr. Young. The pilot project I kicked off in my Congressional district last week will serve as a model recruitment drive for our nation. It encourages the community and businesses to come together to defray the cost of HLA typing. Still, I believe the federal government should play a role in building the registry, especially in increasing the number of volunteers from the variety of ethnic groups we just discussed. I understand that the Institute has many varying demands for its resources, but if this Committee can find additional resources to defray the cost of HLA typing, do you see a federal role in recruiting volunteers?

Dr. Lenfant. Yes, in my personal view, clearly there is a Federal role in recruiting bone marrow donors and defraying the cost of HLA typing, but it must be a role that we continue to share with private organizations and groups. The National Bone Marrow Registry is a national research resource that not only helps individual victims of disease, but can be used as a research tool in finding ways to save even more lives, or perhaps even to prevent disease. As a national research resource, the Registry will need to include various racial and ethnic groups in numbers that reflect their proportionate share in the general population, and the Federal government is in a very good position to help make that happen.

Mr. Young. Dr. Lenfant, the Committee added funds to your budget request last year to allow you to expand research efforts at the NIH utilizing the national registry. You are primarily a research organization and the National Marrow Donor Program is primarily an effective service organization. How do you believe we should link the two?

Dr. Lenfant. The Institute has responsibility for research on blood diseases, and for the use of blood and blood products and the management of blood resources. Although marrow transplantation from related or unrelated donors is feasible and, indeed, saves lives, it is a relatively new mode of therapy and there are many aspects that require further research to improve the overall results. The National Marrow Donor Program's registry, on the other hand, is a rich resource because it gives access to data useful for both basic and clinical research that will contribute significantly to the Institute's mission. However, its utility as a national research resource depends on the extent to which potential donors adequately represent certain ethnic and racial groups, and how the samples are collected, typed, and managed. The National Marrow Donor Program's continued effectiveness as a service organization depends in part on research to improve the effectiveness of the bone marrow transplantation technique. Our program, in turn, is dependent on the availability and quality of the clinical material used in this research.

Mr. Young. Dr. Lenfant, the Board of Directors of the National Marrow Donor Program met in my Congressional District last week. The meeting brought together from throughout our nation outstanding leaders and researchers in the field of bone marrow transplantation. They are excited about the potential new strides we can make in medical research utilizing the national registry. How do you view the research needs in the field of bone marrow biology and bone marrow transplantation?

Dr. Lenfant. Bone marrow transplantation is an effective and accepted therapy for an increasing number of diseases of the bone marrow and the immune system. Bone marrow transplants differ from most tissue or organ transplants in that bone marrow contains cells with an ability to develop immune responses. Although the field of bone marrow transplantation has been developing rapidly, many opportunities remain.

Much research needs to be done to improve the results of bone marrow transplantation from donors. The four major problems in marrow transplantation are 1) graft failure, either early (primary) or late (secondary); 2) reaction of the transplanted marrow against the recipient (graft-vs-host disease); 3) stimulation or maintenance of graft-vs-leukemia effect, when the purpose of the transplant is to treat leukemia; and 4) cost and laboratory capacity for HLA typing of donors.

Basic research is needed to isolate and culture primitive stem cells, the precursors of all blood cells, in order to learn more about their basic biology and responses to various new growth factors. These studies will help improve the success of bone marrow grafts. This basic research may also lead to the harvesting of these cells from the blood where they circulate in small numbers. "Marrow" donation could then consist of an apheresis procedure, done in a few hours, obviating the need for hospitalization, general or spinal anesthesia, and time in an operating room. Growing large numbers of these cells in test tubes could improve the chances for a successful graft and speed the recovery of marrow function. Further development of techniques to grow and especially to preserve stem cells will permit marrow or peripheral stem cells to be harvested before the patient-recipient's bone marrow is destroyed. Stem cells are found in relatively large numbers in umbilical cord blood, most of which is now discarded. It is possible that umbilical cord stem cells could cause fewer complications when transplanted, so that HLA matching need not be so exact. If so, a bank could be established where HLA typed stem cells are frozen, to be used as a transplant when needed. Most of these studies must be done on blood or marrow from donors, with later testing in marrow recipients.

Additional research is needed on the factors influencing the occurrence of graft-vs-host disease, which causes major morbidity and mortality in the bone marrow recipient. It is important to learn whether the factors that influence the occurrence of the beneficial anti-leukemic (graft-vs-leukemia) effect are related to those that produce graft-vs-host disease. The relationship of these phenomena to HLA types and matches and the immunologic events involved in their expression need to be delineated. Reducing T-cells (one kind of white blood cell) in marrow to be grafted seems to reduce the frequency and severity of graft-vs-host disease, but only at the cost of diminishing the likelihood of a successful graft and the beneficial graft-vs-leukemia effect. Additional research may overcome some of these problems. Clinical trials are needed to evaluate the results obtained with different T-cell depletion techniques and to compare T-cell depletion with other approaches to the control of graft-vs-host disease. This research may ultimately lead to better graft success rates, reduced or eliminated graft-vs-host disease, and enhanced preservation of the graft-vs-leukemia effect, where desirable.

Methods for HLA typing need to be refined and automated, where possible, to improve test reliability and increase laboratory volume. New methods of HLA typing need to be developed to define the subtle differences in donor and recipient types that remain undetected using the present technology, and may result in graft rejection and graft versus host disease. Further, results from these new techniques must be compared with those from standard serological procedures. The NMDP repository of cells for donor-recipient pairs will be invaluable for these studies. This research will permit faster and more accurate HLA typing, especially for minorities where current techniques are often inadequate. It will also permit separation of clinically important molecular differences from those of little or no importance, permitting careful matching for the former and little concern for the latter. Controlled clinical trials will be needed to confirm the experimental results.

The NHLBI plans to establish a clinical bone marrow transplant (BMT) unit in the NIH Clinical Center. The availability of a dedicated facility for BMT would enable intramural scientists to extend findings from their basic research laboratories and attempt innovative, experimental, therapeutic interventions for specific diseases. The possibility of treating genetic diseases through modifying the genome of somatic cells by gene insertion seems likely to be achieved in the next several years. It is probable that such experimental treatment will occur initially in the context of BMT. The development of a BMT facility at the Clinical Center will enable intramural scientists to assume a leading role in the development of such BMT applications. Most of the published clinical research in bone marrow transplantation has relied upon historical or previously published studies for patient comparison groups. Although information derived from such studies can be useful, contemporary comparisons will be needed before conclusions can be regarded as firm. The intramural bone marrow transplant program may be able to stimulate such controlled clinical research through leadership and example.

The NHLBI will expand its National Blood Resource Education Program (NBREP) to include public and professional education about BMT. Considerable media attention has been given to the plight of individual patients for whom donors are difficult to find, and a number of patient-focused, crisis donor recruitment drives have been undertaken. Measure need to be taken to ensure that prospective donors provide informed consent and meet certain requisite health criteria, and that samples are collected properly and efficiently. Give the prospects for expanded interest in bone marrow donation, an educational effort is essential to address these needs. NBREP will especially focus on educating minorities to the needs for marrow donors to make the program a resource for all Americans.

BONE MARROW RESEARCH

Mr. Young. Dr. Lenfant, it's my understanding that you are in the process of establishing a special bone marrow research program within your Institute. What are your plans for this program and are funds budgeted for this research?

Dr. Lenfant. Bone marrow stem cells are rapidly dividing cells that are the source of all bone marrow cells and the cells that circulate in the blood. As such, they are an excellent vehicle for introducing a desired gene into patients with genetic diseases. We plan to establish a gene therapy/bone marrow transplantation unit in the Clinical Center. We would like to devote 4 to 8 beds of one nursing unit to transplantation and utilize the 12 to 14 beds for intermediate and standard nursing care for these, and all other, patients of the hematology service. Specific research protocols would be targeted to genetic diseases such as sickle cell disease, aplastic anemia, alpha-1-antitrypsin deficiency and adenosine deaminase deficiency.

In addition to the bone marrow transplantation unit, we plan to expand basic research to develop methods to separate bone marrow stem cells from all other bone marrow cells, particularly cancer cells and cells that can cause immunological rejection of the bone marrow graft, which is presently a major problem. We will also seek ways of growing stem cells in the laboratory so that larger amounts will be available for transplantation.

Expansion of our non-human primate facility will be necessary in order to carry out the animal research that is required before initiating research protocols for human patients.

The Institute has included some funds in the 1991 budget for these programs. Should additional funds become available, the Institute would begin more rapid development and earlier implementation of the clinical portion of this program.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

FY 1991 Budget — Page No.

Appropriation language and explanation of language changes.. 170

Amounts available for obligation........................... 171

Budget mechanism table..................................... 172

Crosswalk tables... 174

Summary of changes... 177

Budget authority by activity............................... 179

Budget authority by object................................. 180

Significant items in House and Senate Appropriations Committee reports.......................... 182

Authorizing legislation.................................... 187

Appropriations history..................................... 188

Justification:

A. General statement.................................. 191
B. Program accomplishments............................ 194
C. AIDS research program.............................. 207
D. Heart and vascular diseases program................ 212
E. Lung diseases program.............................. 222
F. Blood diseases and resources program............... 229
G. Intramural research................................ 236
H. Research management and support.................... 242
I. Detail of permanent positions...................... 245
J. Advisory and assistance............................ 247

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

For carrying out sections 301 and 1105 and title IV of the Public Health Service Act with respect to cardiovascular, lung, and blood diseases, and blood and blood products [$1,091,264,000] $1,112,502,000.

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1989.)

NATIONAL INSTITUTES OF HEALTH

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation	$1,059,303,000	$1,091,264,000	$1,112,502,000
Enacted administrative reductions	-13,318,000	-3,740,000	---
Sequester order	---	-15,170,000	---
Subtotal, adjusted approppppriation	1,045,985,000	1,072,354,000	1,112,502,000
Real transfer to the Office of the Assistant Secretary for Health for AZT grants	-476,000	---	---
Comparative transfer to:			
Division of Research Resources for administrative cost of RCMI Program	-34,000	---	---
Fogarty International Center for passport activities	-19,000	-19,000	---
Comparative transfer from:			
Office of the Director, NIH for additional FTEs	803,000	---	---
Subtotal, adjusted budget authority	1,046,259,000	1,072,335,000	1,112,502,000
Unobligated balance, start of year	---	---	---
Unobligated balance, end of year	---	---	---
Unobligated balance, lapsing	-1,000	---	---
Total Obligations	1,046,258,000	1,072,335,000	1,112,502,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1989 - $4,570,000; 1990 - $2,863,000; 1991 - $2,900,000.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Budget Mechanism
(Dollars in thousands)

	1989 Actual		1990 Appropriation 1/		1991 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects						
Noncompeting..........	2,197	$507,315	2178	$520,848	2057	$518,585
Admin. suppl..........	(34)	1,384	(60)	3,920	(60)	3,676
Competing						
Renewal............	261	70,480	267	78,038	326	100,821
New................	418	77,548	319	66,373	374	78,037
Supplemental........	19	1,661	15	1,102	18	1,078
Subtotal, competing...	698	149,689	601	145,513	718	179,936
Subtotal, res. proj..	2,895	658,388	2,779	670,281	2,775	702,197
Research Centers						
Spec./comp. ctrs......	64	87,870	64	86,265	64	86,295
Other research						
Res. career program...	391	25,564	410	27,753	410	27,753
Coop. clin. research..	14	3,544	14	2,737	14	2,737
Minority biom. res....		2,368		2,418		2,624
Other res. related....	124	8,048	112	7,062	112	7,012
Subtotal, other res.....	529	39,524	536	39,970	536	40,126
Total, research grants....	3,488	785,782	3,379	796,516	3,375	828,618

Training						
Individual awards:						
Noncompeting	118	3,427	101	2,833	118	3,543
Competing						
Renewal	1	30	---	---	---	---
New	69	1,952	124	3,617	107	2,909
Subtotal, individual	188	5,409	225	6,450	225	6,452
Institutional awards:						
Noncompeting	1,310	30,936	887	25,306	1,259	34,220
Competing						
Renewal	117	3,203	430	10,680	110	2,988
New	13	356	82	2,038	30	816
Subtotal, institutional	1,440	34,495	1,399	38,024	1,399	38,024
Total, training	1,628	39,904	1,624	44,474	1,624	44,476
Research & development contracts	228	96,720	242	95,310	242	95,484
	FTEs		FTEs		FTEs	
Intramural research	412	77,459	412	85,127	424	92,621
Research management and support	430	46,394	422	48,596	431	51,303
Extramural construction		---		2,312		---
Total	842	1,046,259	834	1,072,335	855	1,112,502
(HIV/AIDS)	(18)	(38,611)	(23)	(42,056)	(35)	(44,463)

1/ Includes approximately $2,312,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

CROSSWALK - 1989 Actual
(Dollars in thousands)

	Research Grants			Training Programs		Research and		Research		
	Research Projects	Research Centers	Other Research	Individual	Institutional	Development Contracts	Intramural Research	Management & Support	Extramural Construction	Total
Heart and vascular diseases program......	$433,665	$37,553	$21,881	$3,643	$21,018	$63,944				$581,704
Lung diseases program......	115,872	26,975	10,002	811	8,572	9,169				171,401
Blood diseases and resources program......	108,851	23,342	7,641	955	4,905	23,607				169,301
Intramural research.....							$77,459			77,459
Research management and support..								$46,394		46,394
Construction...									---	---
Total........	658,388	87,870	39,524	5,409	34,495	96,720	77,459	46,394	---	1,046,259

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

CROSSWALK - 1990 Appropriation 1/
(Dollars in thousands)

	Research Grants			Training Programs		Research and		Research		
	Research Projects	Research Centers	Other Research	Individual	Institutional	Development Contracts	Intramural Research	Management & Support	Extramural Construction	Total
Heart and vascular diseases program......	$436,754	$40,875	$20,638	$4,565	$23,722	$56,581				$583,135
Lung diseases program......	118,706	24,002	10,263	1,285	9,151	12,429				175,836
Blood diseases and resources program......	114,821	21,388	9,069	600	5,151	26,300				177,329
Intramural research.....							$85,127			85,127
Research management and support..								$48,596		48,596
Construction...									2,312	2,312
Total........	670,281	86,265	39,970	6,450	38,024	95,310	85,127	48,596	2,312	1,072,335

1/ Includes approximately $2,312,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

CROSSWALK - 1991 Congressional Justification
(Dollars in thousands)

	Research Grants			Training Programs		Research and		Research		
	Research Projects	Research Centers	Other Research	Individual	Institutional	Development Contracts	Intramural Research	Management & Support	Extramural Construction	Total
Heart and vascular diseases program......	$457,857	$40,875	$20,745	$4,565	$23,722	$56,581				$604,345
Lung diseases program......	125,326	24,002	10,316	1,287	9,151	16,617				186,699
Blood diseases and resources program......	119,014	21,418	9,065	600	5,151	22,286				177,534
Intramural research.....							$92,621			92,621
Research management and support..								$51,303		51,303
Construction...									---	---
Total........	702,197	86,295	40,126	6,452	38,024	95,484	92,621	51,303	---	1,112,502

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Summary of Changes

1990 Estimated budget authority..............................	$1,072,335,000
1991 Estimated budget authority..............................	1,112,502,000
Net change..	+40,167,000

	1990 Current Estimate Base		Change from base	
Changes:	Pos. (FTEs)	Budget Authority	Pos. (FTEs)	Budget Authority
A. Built-in:				
1. Within grade increase.....		$45,319,000		+$717,000
2. Annualization of January 1990 pay raise..........		45,319,000		+402,000
3. 1991 pay raise............		45,319,000		+1,569,000
3. One extra day of pay......		45,319,000		+166,000
4. Federal Employees Compensation Fund.......		45,319,000		+6,000
5. Unemployment compensation fund increase...........		31,000		+3,000
6. FTS rate increase.........		539,000		+20,000
7. Payment for centrally furnished services......		48,902,000		+2,600,000
8. Increased cost of laboratory materials and other supplies......		39,502,000		+1,401,000
9. DHHS Working Capital Fund..		824,000		-45,000
Subtotal................				+6,839,000
B. Program:	No.	Amount	No.	Amount
1. Research projects:				
a. Noncompeting........	2,178	524,768,000	-121	-2,507,000
b. Competing...........	601	145,513,000	+117	+34,423,000
Total................	2,779	670,281,000	-4	+31,916,000
2. Research centers..........	---	86,265,000	---	+30,000

Summary of Changes--continued

	1990 Current Estimate Base		Change from base	
	No.	Amount	No.	Amount
3. Other research............	---	39,970,000	---	+156,000
4. Individual training awards	---	6,450,000	---	+2,000
5. Research and development contracts...............	---	95,310,000	---	+174,000
6. Extramural construction...	---	2,312,000	---	-2,312,000
	Pos. (FTEs)	Budget Authority	Pos. (FTEs)	Budget Authority
7. Intramural research.......	412	85,127,000	12	+2,712,000
8. Research management and and support.............	422	48,596,000	9	+650,000
Subtotal................				+33,328,000
Total changes.........				+40,167,000

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Budget Authority by Activity
(Dollars in thousands)

	1989 Actual		1990 Appropriation 1/		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Heart and vascular diseases program........	---	$581,704	---	$583,135	---	$604,345
Lung diseases program.....	---	171,401	---	175,836	---	186,699
Blood diseases and resources program.......	---	169,301	---	177,329	---	177,534
Intramural research.......	412	77,459	412	85,127	424	92,621
Research management and support.............	430	46,394	422	48,596	431	51,303
Extramural construction...	---	---	---	2,312	---	---
Total Budget Authority..	842	1,046,259	834	1,072,335	855	1,112,502
(HIV/AIDS)..............	(18)	(38,611)	(23)	(42,056)	(35)	(44,463)

1/ Includes approximately $2,312,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Total number of full-time permanent positions	677	690	+13
Total compensable work years:			
Full-time employment	850	871	+21
Full-time equivalent of overtime and holiday hours	6	6	---
Average ES salary	$79,306	$82,082	+$2,776
Average GM/GS grade	9.3	9.3	---
Average GM/GS salary	37,735	39,056	+1,321
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	69,280	71,705	+2,425
Average salary of ungraded positions	22,483	23,270	+787
Personnel compensation:			
Full-time permanent	$26,987,000	$28,760,000	+$1,773,000
Other than full-time permanent	7,691,000	8,222,000	+531,000
Other personnel compensation	1,581,000	1,686,000	+105,000
Special personnel service payments	1,486,000	1,590,000	+104,000
Total personnel compensation	37,745,000	40,258,000	+2,513,000
Personnel benefits	7,574,000	7,921,000	+347,000
Benefits for former personnel	31,000	31,000	---
Travel and transportation of persons	1,249,000	1,261,000	+12,000
Transportation of things	194,000	198,000	+4,000

	1990 Appropriation	1991 Estimate	Increase or Decrease
Rent, communications, and utilities..	2,173,000	2,226,000	+53,000
Printing and reproduction............	1,800,000	1,800,000	---
Other services:			
Project contracts..................	95,310,000	95,484,000	+174,000
Centrally furnished services.......	46,662,000	49,747,000	+3,085,000
Standard level user's charge.......	2,240,000	1,755,000	-485,000
Other..............................	19,567,000	23,790,000	+4,223,000
Supplies and materials...............	7,477,000	7,711,000	+234,000
Equipment............................	7,011,000	7,226,000	+215,000
Grants, subsidies, & contributions...	843,302,000	873,094,000	+29,792,000
Total budget authority by object...	1,072,335,000	1,112,502,000	+40,167,000

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Significant Items in House Appropriations Committee Report

Item	Action taken or to be taken
1990 House Report	
1. "The Committee is aware of the great strides that have been made in establishing a National Bone Marrow Donor Program. ...the Committee believes the highest priority should be given to funding the third year of the contract for the operation of the registry, assimilating a number of independent international registries into the national registry, and funding research programs and activities specifically related to the registry." (page 55)	1. The NHLBI has assumed the important responsibility for the National Bone Marrow Donor Program and will provide adequate support for the contractors maintaining and expanding the registry and conducting research related to bone marrow transplantation.
2. "Asthma is an increasing cause of morbidity and mortality. ... At the basic science level, an initiative for stimulating cellular and molecular biologic research into the influences of the autonomic nervous system upon airway function in health and disease is under consideration. The Committee is fully supportive of expanded efforts in this area." (page 56)	2. The NHLBI gives high priority to expanded asthma research. In FY 1990, the Institute will support initiatives on beta-adrenergic modulation of airway function and interventions for control of asthma among black and Hispanic children.
3. "The Preventive Cardiology Academic Award is made to schools of medicine and osteopathy, is designed to foster the initiation of and improvement in preventive cardiology curricula and to stimulate research careers in the area of primary prevention of cardiovascular disease. Given the prevalence of cardiovascular disease in the minority population, the Committee is concerned that no Preventive Cardiology Academic Awards have been made to an Historically Black College or University. The Committee urges NHLBI to review the program's guidelines and make an effort to identify barriers faced by HBCUs." (page 56/57)	3. The NHLBI has made special efforts to solicit applications from institutions with significant minority populations and anticipates that several of these applications will successfully compete for funding.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Significant Items in Senate Appropriations Committee Report

Item	Action taken or to be taken
1990 Senate Report	
1. "The Committee has generally been pleased with the historical commitment of the NHLBI to health promotion and disease prevention research... The Committee expresses concern, however, that last year NHLBI decreased its percentage of expenditures in this area. The Committee remains committed...to having NHLBI increase both behavioral research and education campaigns... The Committee further urges NHLBI to increase the number of behavioral scientists on its various study sections and other policy oriented boards and committees. The Committee strongly feels that behavioral research is an area in which NHLBI should develop cooperative initiatives with other NIH Institutes such as the NCNR and NIA." (page 114)	1. The National Heart, Lung, and Blood Institute is fully committed to health promotion disease/prevention research and recognizes the importance of education programs to disseminate critical information about behavior modification to the public. The NHLBI will seek to increase spending to the extent to which available funds permit. The NHLBI continues to look to the behavioral sciences to further its mission and has moved to ensure that this area is properly represented on initial review groups and advisory committees. The NHLBI has collaborated with both the NCNR and the NIA in the past and will continue to look for future opportunities to do so.
2. "A recent Institute-sponsored trial showed that, with the use of thrombolytic agents and other current therapy, immediate or early coronary angiography and balloon dilatation offer no additional benefit to the already good prognosis of patients whose symptoms stabilize. The Committee urges the NHLBI...to get such information into general medical practice." (page 114)	2. The NHLBI has begun planning for and will implement its National Heart Attack Early Action Program, which is intended to transmit this kind of information directly to health care practitioners.

Item	Action taken or to be taken
3. "The Committee is very supportive of the lung health study a clinical trial being conducted by NHLBI that will determine if individuals at risk for the development of chronic obstructive pulmonary disease can avoid it through a series of preventative intervention strategies, including the use of certain bronchodilator medications... The Committee would like to receive a written report from NHLBI on the status of this trial before the next budget cycle." (page 115)	3. The NHLBI submitted a report on the COPD clinical trial to NIH on November 22. The Institute expects this report to be transmitted to Congress in an expedious manner.
4. "The Committee has provided sufficient funds above the President's request to continue the operation and development of the National Marrow Donor Program and fully expects the program be given top priority....the Committee concurs with the Department's view expressed in the March report that critical to the effective functioning of the National Marrow Donor Program is "flexibility in the governance of the registry, as reflected in the active involvement of private groups that are interested in the establishment of a national registry..." It is the Committee's expectation that the Director of the NHLBI will facilitate the involvement of such groups, as well as foster and maintain a close working relationship with these groups in the management of the registry." (page 116/117)	4. The NHLBI has assumed the mission of the National Bone Marrow Donor Program and has given it top priority. The Institute's position is that the participation of all organizations involved with the National Marrow Donor Registry is best for the Program. To this end, the Institute has met on numerous occasions with many individuals and organizations to solicit their views and help, and will continue to facilitate the broadest possible participation in the administration of the Program.

Item	Action taken or to be taken
5. "The Committee is pleased to learn that a number of nurses and national nursing organizations presently serve in the NHLBI extramural divisions and offices...in research and policy planning activities....The committee is aware that nurses are being considered routinely for administrative and advisory positions...and urges that NHLBI continue its efforts in this area, as well as expand the number of committees on which nurses serve. Further, the Committee strongly supports the continued involvement of nurse researchers in research projects sponsored by NHLBI, as well as the opportunity for nurses to apply for pre- and post-doctoral training. The Committee urges NHLBI to continue its efforts to ensure that professional nurses remain actively involved in its activities and programs." (page 118)	5. The NHLBI continues to stress the importance of the nursing profession in carrying out the mission of the Institute. The NHLBI is committed to ensuring that a nursing perspective is obtained for both policy and research initiatives. The Institute has nurses in key staff positions and has successfully sought representation from the nursing profession for membership on its Council and advisory committees.
6. "The Committee encourages the National Heart, Lung, and Blood Institute to support cardio-vascular research which will improve vascular surgical techniques by developing a greater understanding of how blood vessel prostheses (grafts) behave in the body." (page 115)	6. The NHLBI is pleased to report that there are significant results related to this area which are described in this document.
7. "The Committee is pleased that the question of optimal long-term management of mild hypertension is receiving new attention. Of particular interest are therapies that avoid or minimize drug treatment, including weight loss, relaxation regimens, dietary restriction of alcohol and sodium, and dietary supplementation with potassium, calcium, or magnesium." (page 115)	7. Basic research supported by NHLBI should eventually lead to identifying individuals at risk for developing hypertension and predicting patient response to specific therapies, including non-pharmacologic approaches.

Item	Action taken or to be taken
8. "The Committee has learned of the many research opportunities available to develop an oral chelator to reduce the overload of iron deposits in vital organs caused by necessary numerous blood transfusions to patients with some anemias, and especially Cooley's anemia....The Committee strongly urges funding of eligible grant proposals and the activation of any other mechanisms which might cause the research to move more rapidly; funds have been made available to the institute to carry out this program." (page 116)	8. The Institute has a balanced portfolio of research projects to develop iron chelators and will continue to give this research high priority. In addition, the Institute is preparing clinical protocols to evaluate iron chelators as soon as they are developed.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Authorizing Legislation

	PHS ACT/ Other Citation	U.S. Code Citation	1990 Amount Authorized	1990 Appropriation	1991 Amount Authorized	1991 Budget Estimate
esearch and Investigation........	Section 301	42§241	Indefinite	$1,026,861,000	Indefinite	$1,068,026,000
ational Heart, Lung, and Blood Institute......................	Title IV, Parts B and C	42§284c	Such Sums as Necessary		2/	
ational Research Service Awards..	Section 487	42§288	Such Sums as 1/ Necessary	$44,474,000	1/ 2/	$44,476,000
Total Budget Activity...........				$1,072,335,000		$1,112,502,000

1/ This training authority is shared with the research training programs of the Alcohol, Drug Abuse, and Mental Health Administration.

2/ Authorizing legislation to be requested.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1982	$510,050,000 2/	$582,831,000	$585,741,000	$559,637,000
1983	577,143,000	621,977,000	626,540,000	624,259,000
1984	639,774,000	667,601,000 3/	685,231,000 3/	704,939,000
1985	718,852,000	764,135,000 4/	807,149,000	805,269,000
1986	775,254,000	853,088,000 5/	863,652,000	859,239,000
1986 Sequester				-36,947,000
1987 6/	785,697,000	921,410,000	921,502,000	930,001,000
1988	821,887,000	990,808,000 7/	990,646,000	965,536,000
1989	1,015,471,000 8/	1,018,903,000	1,056,003,000	1,045,985,000
1990	1,039,846,000 9/	1,090,930,000	1,091,597,000	1,087,524,000 10/
1990 Sequester				-15,170,000
1991	1,112,502,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Reflects the September amendment; the original request was $579,602,000.

3/ Excludes $28,490,000 in NRSA training programs not considered.

4/ Excludes $27,999,000 in NRSA training programs requested but not considered.

5/ Excludes $40,206,000 in NRSA training programs and $3,300,000 in construction not considered.

189-190

6/ The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House Allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate Allowance and the Appropriation spread the funding among the Institutes, including $17,091,000 for NHLBI.

7/ Does not include funding for AIDS research consolidated at the Secretary's level.

8/ Excludes funds for AIDS research and education ($39,032,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

9/ The 1990 request excludes funds for the National HIV program ($42,651,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

10/ Excludes enacted administrative reduction of $3,740,000.

Justification

National Heart, Lung, and Blood Institute

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
TOTAL..	834	$1,072,335,000	855	$1,112,502,000	+21	+$40,167,000
AIDS...	(23)	(42,056,000)	(35)	(44,463,000)	(+12)	(+2,407,000)

General Statement

The National Heart, Lung, and Blood Institute (NHLBI) provides leadership for a national program in diseases of the heart, blood vessels, lungs, and blood, and in the uses of blood and in the management of blood resources. Through its intramural and extramural programs, the NHLBI conducts and supports an integrated research program that includes basic research, clinical trials, epidemiologic, and demonstration and education projects that relate to the causes, diagnosis, treatment, and prevention of heart, blood vessel, lung, and blood diseases. The program also includes studies of the clinical uses of blood and all aspects of the management of blood resources. In addition, the NHLBI supports research training of new investigators and the career development of established researchers in both basic and clinical research related to heart, blood vessel, lung, and blood diseases and transfusion medicine.

While progress has been made in each of the program areas of the Institute, the diseases within the purview of the NHLBI continue to impose a heavy burden on the health and economy of the American people. Cardiovascular, lung, and blood diseases accounted for 1,171,000 deaths in 1988 or 54 percent of all deaths. They represent 5 of the 10 leading causes of death, 5 of the 10 leading causes of infant death, and 5 of the 13 leading chronic conditions that result in varying degrees of limitations of activity. Cardiovascular diseases alone were responsible for approximately 45 percent of all deaths in 1988. Diseases of the lungs, with the exception of lung cancer, caused an estimated 194,000 deaths in 1988. Disorders of blood frequently are contributing factors in death from other diseases such as a heart attack, and they also cause disabling and fatal diseases such as Cooley's anemia and sickle cell anemia.

The economic costs of diseases of the heart, blood vessels, lungs, and blood is staggering. In 1987 they resulted in nearly $176 billion in economic costs, or nearly 24 percent of the total economic costs of all illnesses and premature deaths. This cost estimate represents $83 billion in direct health care expenditures, $33 billion in indirect costs of lost productivity due to illness, and $60 billion in indirect costs that result from lost productivity due to premature death.

The search for new knowledge about disease processes and improved methods of diagnosis and treatment has led to important advances against heart, blood vessel, lung, and blood diseases. Over the past 20 years there have been significant declines in mortality from cardiovascular and blood clotting diseases. The overall improvement in mortality from cardiovascular diseases is reflected in the rapid increase in life expectancy in recent years. The downward trend in mortality from these diseases has persisted over the last 20 years and the impact of the decline has been substantial. The age-adjusted rate for all causes of death dropped from 744 deaths per 100,000 in 1968 to 536 per 100,000 in 1988, and 77 percent of the reduction is due to the decline in the death rate from cardiovascular diseases. However, the mortality from chronic obstructive pulmonary disease (COPD) has continued to increase; in fact, the increase in the death rate for COPD was 54 percent for the same 20 year period.

The programs of the Institute have several dimensions. The combination of fundamental research, population based studies, behavior research, and clinical trials is designed to provide a comprehensive approach to developing an understanding of the causes of cardiovascular, lung, and blood diseases, to assist in their diagnosis, and to develop strategies to reduce the related morbidity and mortality. Educational programs are designed to convey this information to health care practitioners and the public.

The Institute's overall objective in integrating basic and clinical research and disseminating information about health care strategies is to reduce the morbidity and mortality of heart, lung, and blood diseases in the United States. This approach has led to many research accomplishments, a few of which are described in the following material.

Budget Policy

The FY 1991 budget request for the Institute favors basic research and totals $1,112,502,000, an increase of $40,167,000 over the comparable FY 1990 level of $1,072,335,000. The request for AIDS funding in the amount of $44,463,000 is included in this request. An important priority within this budget request is an increase in funding for basic research. Continued investment in basic research is essential to innovative clinical applications in the years to come.

The budget request will permit the Institute to fund 2,057 noncompeting research project grants and 718 competing research project grants. The average cost of a noncompeting research project will increase from $239,140 to $252,107, an increase of 5.4 percent. The average cost of a competing research project grant will increase from $242,118 to $250,607, an increase of 3.5 percent.

The Institute will support 64 research centers the same number as supported in FY 1990. The FY 1991 budget request for research centers is $86,295,000, an increase of $30,000 over FY 1990 for AIDS related research.

The FY 1991 request includes $27,753,000 for research career programs, the same as the FY 1990 level. It also includes $12,373,000 for cooperative clinical research, Minority Biomedical Research Support, small instrumentation grants, conference grants, and scientific evaluation. The request includes an 8.5 percent increase for the Minority Biomedical Research Program.

For research training, the FY 1991 budget request is $44,476,000, an increase of $2,000 over FY 1990. The Institute will support 1,624 full time equivalent training positions, the same number as FY 1990.

The FY 1991 request provides $95,484,000 for research and development contracts, an increase over FY 1990 of $174,000. The FY 1991 request for intramural research is $92,621,000, an increase of $7,494,000 over the $85,127,000 available in FY 1990. Of this increase, $2,204,000 is for AIDS related research. For research management and support the FY 1991 request is $51,303,000, an increase of $2,707,000 over the $48,596,000 available in FY 1990. Of this increase, $246,000 is for AIDS related activities. Both intramural research and research management and support include funds for an increase of 12 AIDS FTEs and 9 other FTEs.

The President's Budget does not include funds for construction or renovation of extramural research facilities. The amount in this account which was earmarked in FY 1990 for facilities construction was $2,312,000.

Program Accomplishments

The Institute promotes an integrated program of basic and clinical research and believes that the advances made in basic research will provide a foundation for the development of new therapeutic and preventive strategies that will be tested in the clinical environment. In addition, clinical observations often stimulate fundamental research. One highly successful vehicle for integrating basic and clinical sciences is the Institute-sponsored series of symposia entitled "Frontiers in Basic Sciences That Relate to Heart, Lung, and Blood Diseases". The symposia are designed to bring together basic scientists and clinicians to capitalize on and to transfer the progress achieved in basic science disciplines to clinical research problems. In the past year, the Institute sponsored two symposia, one entitled "The Biology of Tissue Transplantation" and the other entitled "Thrombolysis". Additional symposia, one on "Vascular Biology and Medicine" and another on "Cell-Cell Interactions" are being planned for next year.

The Institute has a strong commitment to fundamental research and has identified a need to expand its research efforts in the application of molecular biology. The Institute's Programs of Excellence in Molecular Biology were established to combine molecular biology research with basic heart, lung, and blood research and to provide opportunities for investigators in the areas of heart, lung, and blood research to become skilled in the experimental strategies, approaches, and techniques of molecular biology.

Basic research that seeks new knowledge also attempts to apply our understanding of biological phenomenon to the treatment of disease. For example, basic research has led to the development of a strain of laboratory mice whose blood cells make human hemoglobin. Now that it has been shown possible to produce a transgenic mouse with normal hemoglobin genes, it should be possible to implant defective hemoglobin genes, such as those that cause sickle cell disease and other blood diseases. If successful, scientists will for the first time have available animal models that will not only allow detailed study of hemoglobinopathies but also permit explorations of new approaches to treatment.

To validate the safety and efficacy of new preventive, diagnostic, and therapeutic strategies before they are available for routine clinical practice, the Institute supports several clinical trials and clinical research protocols. The pediatric medical community has long been concerned about the increased incidence of cerebral dysfunction among newborns with severe cyanotic congenital heart disease. Many such infants undoubtedly experience significant brain damage prior to corrective surgery, but may be subject to further insult during the peri-operative period. The Institute is supporting a trial to compare the confluence of two surgical anesthetic techniques, hypothermia with circulatory arrest and hypothermia with low-flow bypass, to see if either of them offers neurologic and developmental benefits to the affected children.

After new information has been acquired and health care strategies have been validated, the information is ready for transfer to physicians, other health care personnel, and the general public. This task is the responsibility of the Office of Prevention, Education, and Control. The office develops educational and informational materials about clinical applications of research results and disseminates scientific and technical information about heart, blood vessel, lung, and blood diseases for the public and health practitioners. The National High Blood Pressure Education Program, the National Cholesterol Education Program, the NHLBI Smoking Education Program, and National Blood Resource Education Program are major ongoing efforts of Institute and are designed to provide information about these areas to health care practitioners, patients, and the public. In the past year, a major new education effort on asthma, the National Asthma Education Program, was initiated to educate patients, health professionals, and the public about current approaches to the diagnosis and treatment of asthma.

Basic Research

Patent ductus arteriosus (PDA) is a developmental disorder that affects the ductus arteriosus, a blood vessel that links the pulmonary artery to the aorta in the fetus. In normal development, the vessel is open during gestation but closes permanently shortly after birth. In patent ductus arteriosus, closure fails to occur. In the hereditary form of PDA, surgical correction is usually required. Recent studies of normal ductus arteriosus in dogs have shown that normal closure of the vessel is accompanied by a large increase in hyaluronic acid (HA), a complex carbohydrate that is a normal constituent of blood vessel walls. However, in hereditary canine PDA, the normal increase in HA synthesis does not occur. It therefore appears that hereditary PDA may be associated with a genetic defect that blocks the synthesis of HA. If the genetic defect can be positively identified, it may be possible to develop a method of prenatal diagnosis for PDA even though it only manifests itself after birth. In addition to the improved prospects for understanding and perhaps preventing PDA, the findings regarding the role of HA may have implications for the growth and development of normal blood vessels.

The sleep apnea syndrome is a well recognized clinical disorder which results in apnea, periodic breathing, hypoxemia, hemodynamic changes, and excessive daytime sleepiness, and may lead to potentially life threatening health consequences. Since most sleep apnea patients breathe normally while awake, the mechanisms responsible for respiratory control during sleep are likely to be mediated, in part, by the brain. Basic progress has been made in understanding the neural mechanisms responsible for apnea during rapid eye movement (REM) sleep, a period of sleep marked by very irregular respiratory activity and increased upper airway resistance. While studies have shown that there is a general loss of muscle tone and a decrement in skeletal muscle activity during REM sleep, it was previously thought that it did not occur in the diaphragm muscle. It is now known that the diaphragm muscle experiences a loss of neural drive during sleep, suggesting that it too is susceptible to a loss of muscle tone that may explain some of the variability in breathing during sleep. In addition, a new pharmacological model of REM sleep has shown that muscle tone in the upper airway can be affected by neurological mechanisms in the hind brain. These new findings have advanced our understanding of the pathophysiology of sleep apnea and provided important new directions for research.

Recent developments in research on gene transfer and in utero transplantation offer the prospect of major advances toward effective in utero therapy for the hemoglobinopathies and other genetic diseases. While only one in ten thousand cells in the bone marrow is a stem cell, it is the stem cells that give rise to all of the circulating blood cells. Consequently effective transfer and expression of stem cells is one likely path for effective genetic therapy. Significant progress has now been reported toward long-term engraftment of hematopoietic stem cells in sheep and monkeys. When examined four years after the date of transplantation, no evidence of graft-versus-host disease, either overt or subclinical, was detected in any of the monkeys or long-term surviving sheep. The long term success of these transplants suggest that all of the potential technical problems related to successful fetal-to-fetal transplant of hematopoietic stem cells in humans may have been overcome. Experiments are currently in progress to assess the applicability of in utero transplantation to treat a sheep model for Batten's disorder, a neurological disorder involving lipid storage problems that affects sheep in a manner quite similar to the way it affects humans.

Adult respiratory distress syndrome (ARDS) is a condition of acute respiratory failure that results from a variety of causes. It affects approximately 150,000 individuals each year and is among the most common causes of death from postoperative and major traumas. Life-threatening infections are common complications in patients with ARDS. In order to prevent and treat them, it is necessary to understand the abnormalities in the defense functions of ARDS patients that predispose them to infection. Neutrophils are important cells of the immune system that migrate to the site of infections to fend off invading bacteria. It is currently thought that abnormal neutrophils may contribute to the high rate of serious infection in patients with ARDS. Since the average diameter of neutrophils is larger than the average diameter of pulmonary capillaries, normal neutrophils alter their shape in order to pass through the pulmonary vessels to reach sites of pulmonary infection and inflammation. However, neutrophils from ARDS patients appear to become trapped in the pulmonary capillaries, suggesting an impaired ability to modify their shape. Additional evidence to support this hypothesis has come from animal studies showing that neutrophil retention in the lungs is induced by bacterial endotoxin. Endotoxin concentrations comparable to those in the sera of ARDS patients made neutrophils stiffer and prevented migration in a pulmonary capillary model. Furthermore, data suggest that the mechanism of neutrophil stiffening is related to the cytoskeletal structure within the neutrophil. Thus, it may be possible pharmacologically to counter the stiffening and retention of neutrophils and thereby enhance their ability to migrate to localized sites of inflammation and infection in patients with ARDS.

Platelets play an essential role in thrombosis and are a key factor in determining the efficacy and rate of thrombolysis associated with the administration of thrombolytic therapy. Studies have shown that the binding of an adhesive protein, such as fibrinogen, to a platelet receptor is necessary for platelet aggregation. Investigators also have found that, when activated, a platelet membrane glycoprotein complex, called GP IIb-IIIa, undergoes a change and becomes a receptor for adhesive proteins. Both glycoprotein IIb and IIIa have been cloned, and the common amino acid sequence of the binding site of the adhesive proteins has been determined. Monoclonal antibodies to the platelet receptor are yielding promising results as antithrombotic agents. In addition, peptides mimicking the adhesive site of proteins have been synthesized and are excellent inhibitors of platelet aggregation. The results of these studies are likely to have broad implications for our understanding of the basic biology of adhesion and the reactions between adhesive proteins and their receptors. Such reactions constitute a fundamental process in cell biology that is involved not only in thrombosis but also in such pathological conditions as tumor metastasis and bacterial infection.

Recent findings on the relationship between hypertension and the blood vessels of the brain are providing new insights into the development of stroke. Chronic hypertension produces subtle, but important structural changes in blood vessels in the brain. A comparison of the volume density and cross sectional area of the small arterioles on the surface of the brain in stroke-prone spontaneously hypertensive rats and in normal rats has shown the surprising result that the stiffness of arterioles in the stroke-prone rats is reduced. The reduction in stiffness, which is associated with excessive growth of the vessels, suggests that the mechanics of the vessels may play an important role in the development of stroke. The blood vessels of the area postrema, a region of the brain involved in the control of the cardiovascular system, appear to be related in a different way in the development of stroke. It is thought that the area postrema may sense vasoactive substances like angiotensin and vasopressin, that are involved in both normal control of blood pressure and hypertension. Unlike the endothelial linings of vessels in most other parts of the brain, those in the area postrema allow substances to pass to the surrounding brain stem. As a result, it is speculated that the area postrema may be more sensitive to circulating stimuli and that its blood vessels may respond differently than those with impermeable linings. By exploring the regulation of blood flow to the cerebral hemispheres, the brain stem, and the surface of the brain, studies such as these provide new opportunities for furthering our understanding the impact of hypertension on the brain blood vessels and how hypertension predisposes an individual to stroke.

Clinical Research

Atherosclerotic obstruction of the coronary arteries is a major cause of heart attacks. As plaque develops in the coronary arteries, the blood supply to the heart muscle is restricted. Researchers are increasingly resorting to computer enhanced X-ray studies of the coronary arteries to determine whether the progression of plaque development can be halted or reversed. In one study, men with high levels of circulating serum lipids, a family history of heart disease, and angiographic evidence of advanced coronary disease were randomized among three groups. All of the members of the control group received a placebo and some received the bile acid sequesterant, colestipol. Colestipol was also given to all members of the two treatment groups. However, one treatment group received niacin in addition to the colestipol while the other received lovastatin in addition to the colestipol. Angiograms were taken at the beginning of the study and again two and one-half years later at the conclusion of the study. Marked reductions in LDL and moderate to marked increases in HDL occurred in both treatment groups. Definite lesion progression occurred in 46 percent of the placebo group, while only 11 percent showed definite regression. In contrast, among the treatment groups, lesion progression was only half as common (23 percent) and lesion regression was three times more common (35 percent). Moreover, the frequency of events such as heart attack, death, bypass surgery, and angioplasty during the study was 21 percent in the placebo group as compared to only 5 percent in the treatment groups. The results of this study are the first to show a beneficial effect on coronary heart disease from the recently introduced cholesterol lowering drug, lovastatin. Studies like this one make it clear that by lowering blood cholesterol through a combination of diet and drugs the atherosclerotic process in the coronary arteries can be slowed and even reversed.

Emphysema is characterized by an enlargement of the air sacs, resulting from destruction of alveolar walls. In the lung, the alveoli are the site where oxygen is transferred from the air to the blood. Since alveoli cannot be regenerated, loss of alveoli results in permanent "holes" in the lung. Clinical manifestations of emphysema are shortness of breath, particularly upon exertion, and difficulty in exhaling. An estimated 2 million Americans have emphysema, including 20 to 40 thousand who have an inherited form of the disease. The mechanism underlying destruction of alveolar walls involves an imbalance between proteases, which are enzymes that destroy proteins, and inhibitors of proteases. The most important protease involved in the lungs is elastase and the most important inhibitor of protease is alpha-1-antitrypsin. Individuals with inherited emphysema have a homozygous genetic deficiency of alpha-1-antitrypsin. The first step toward possible gene therapy for alpha-1-antitrypsin deficiency was taken when mouse

T lymphocytes that were engineered to express human alpha-1-antitrypsin were transplanted into mice. The T lymphocytes, which accumulate selectively at specific locations, were shown to augment the levels of alpha-1-antitrypsin in the serum and lung fluids of the transplanted mice. In addition, retroviral mediated gene transfer in human T cells also was shown to produce cells able to secrete alpha-1-antitrypsin. While genetic therapy is not yet possible, these new developments, when coupled with the demonstrated success of plasma derived alpha-1-antitrypsin in entering the lung lining fluid, provide reasonable grounds for belief that an effective gene therapy for alpha-1-antitrypsin deficiency induced emphysema may ultimately be possible.

Leg ulcers are a common complication in patients with sickle cell disease. The Cooperative Study of Sickle Cell Disease, a prospective study initiated in 1979 of 4,500 patients, has followed the incidence, prevalence, and clinical course of leg ulcers for a period of seven years. Based upon the clinical presentation of patients upon entry into the study, the overall prevalence of leg ulcers in patients over ten years of age was two and one-half percent. However, the prevalence rate differs according to the genotype, with the highest prevalence occurring in patients with homozygous sickle cell anemia. Patients with two alpha gene deletions and homozygous sickle cell anemia had a much lower overall incidence of leg ulcerations, confirming an effect on leg ulcerations noted among patients with alpha thalassemia. The overall incidence of leg ulcers experienced by the study population, either before or during the study period was approximately 25 percent. The rates increased with advancing age and were higher in males than in females. The levels of hemoglobin and fetal hemoglobin were indirectly related to the occurrence of leg ulcers. Since the incidence of leg ulcers has not been found to correlate with any other clinical measures, these data suggest that therapies to increase either fetal hemoglobin or steady-state hemoglobin may contribute to the prevention of leg ulcers in sickle cell patients. While the primary intent of the study was to examine the natural history of leg ulcers in sickle cell disease, a number of treatments approaches were reviewed. No differences were found for any of the approaches in terms of either overall healing or reoccurrence rates for leg ulcers.

The recently reported results of an ongoing study suggest that tens of thousands of heart attacks can be prevented. The results reported from the Physician's Health Study compared the effect of alternate-day consumption of aspirin to alternate day consumption of placebo among the trial participants. The participants were selected from U.S. physicians who were aged 40 to 82 in 1982 and had no history of heart disease, stroke, or cancer. Because of clear evidence that the aspirin regimen reduced the incidence of myocardial infarction and a very low probability of obtaining reliable results regarding cardiovascular mortality due to a lower than expected mortality rate among participants, the aspirin component of the study was terminated early. While there was a slight trend to increased stroke, particularly hemorrhagic stroke, among the participants who received aspirin, the trend was not statistically significant. Overall, however, the study has lead to the conclusion that aspirin may be prescribed, with appropriate precautions, for several million men at high risk of developing coronary heart disease.

Each year in the United States, neonatal respiratory distress syndrome (RDS) strikes 40,000 infants. Five thousand of the affected infants die, and another 8,000 develop chronic lung disease. Neonatal RDS is caused by the inability of the lungs of premature infants to make surfactant, a material that helps the lungs to inflate easily and prevents their collapse during expiration. Surfactant is produced in the lungs of a fetus in the last trimester. Recent results have shown that treatment of premature infants with a synthetic surfactant results in a significant improvement in lung function and a reduction in mortality from neonatal RDS. Another surfactant produced from bovine lung has been clinically tested and shown to result in significant improvements in newborns with respiratory distress. Although neither of the surfactant preparations has been licensed, they have both been released under a new program designed to speed potentially life saving treatment to patients who are critically ill with diseases for which there is currently no satisfactory therapy. Successful treatment with surfactant replacements will result in reduced periods of mechanical ventilation and thereby decrease the chances of complications. Future work with these preparations will involve testing their efficacy in treatment of other respiratory conditions of newborns, including pneumonia and acute lung injury.

Technology Development

Recent experiments using genetically-altered endothelial cells suggest that improved methods may soon be available to repair damaged arteries, improve the lifetimes of artificial blood vessels, prevent thrombosis, promote angiogenesis, and deliver therapeutic substances to target tissues. Using a retroviral vector, a bacterial gene (lacz) has been inserted into endothelial cells extracted from the blood vessels of dogs. The genetically-modified cells were grown on the inner surface of synthetic Dacron blood vessels and then grafted to the carotid arteries of the donor dogs. After five weeks, the modified endothelial cells were lining the inner surface of the synthetic vessels and were synthesizing beta-galactosidase, the enzyme encoded by the lacz gene. One clear potential application of the finding is to improve the performance and versatility of prosthetic vascular grafts. By lining their inner surfaces with endothelial cells, it may be possible to prevent thrombosis. Another potential application of the finding is in providing more effective drug delivery. Since endothelial cells line the blood vessel walls and thus maintain a constant contact with the blood, they may be an appropriate target for gene transfer when designing drug delivery systems. Potential therapeutic applications of genetically-modified endothelial cells might include the secretion of vasodilators, angiogenic factors, and inhibitors of thrombosis.

Echocardiography permits the non-invasive measurement of heart structure and function. The manual measurements of cardiac dimensions required by the technology when it was introduced in the 1970s has been replaced in the 1980s by computer assisted cross sectional assessments. Echocardiography is now commonly used by practicing cardiologists to diagnose valvular disease, cardiac structure abnormalities, and left ventricular hypertrophy. Use of the technology in the Institute's Framingham study has led to the surprising conclusion that in elderly, but active and healthy study participants, left ventricular (LV) size is an ominous risk indicator that precedes the development of clinically recognized cardiovascular disease in many elderly. Moreover, the association between increased LV mass and clinical disease is much stronger than the associations between clinical disease and such conventional risk factors as smoking and serum cholesterol level. These findings suggest that pervasive and pathologic changes in left ventricular structure occur in many people during middle age. The discovery of this important risk factor would not have been possible without the dramatic evolution of the technology of echocardiography.

The artificial heart program was initiated by the Institute in 1964 to develop devices to assist or replace the failing heart. Since that time, the program has shown progress in the development of electrically-powered total artificial heart systems, electrically-powered ventricular assist systems, and thermally-powered engines. Soon clinical evaluation of an electrically-powered ventricular assist system will begin, while development of the electrically-powered total artificial heart, and thermally-powered engines continues. As research on these circulatory assist components and systems moves through the various stages of development -- component design and evaluation, system design and evaluation, animal experimentation, reliability assessment, and clinical evaluation -- critical scientific, resource allocation, and ethical decisions must be made. To obtain information that is helpful in making these decisions, the NHLBI will contract with the Institute of Medicine (IOM) for an evaluation of the circulatory assist program that will provide independent, objective, and creditable advice regarding the future directions for the program. Throughout the life of its circulatory assist program, the Institute has remained aware of the broad range of questions and problems necessarily raised by the application of mechanical circulatory devices in patients. The efforts of the IOM will address the full range of such issues, including the likely long term prospects for success of these systems; the cost and use of the technology as a part of future health costs for the United States; the social, psychological, ethical, legal, and economic aspects of use of circulatory assist devices artificial heart; possible technological alternatives; and the importance of the circulatory assist technology to the scientific and economic standing of the United States.

Prevention and Education

In November 1985, the National Cholesterol Education Program (NCEP) was initiated by the NHLBI to help reduce coronary heart disease mortality in the United States by decreasing the prevalence of elevated blood cholesterol. The Program's first efforts were aimed at physician and patient education through the production of comprehensive, detailed recommendations for the proper treatment of high blood cholesterol,and related patient materials. Recommendations for laboratory standardization of cholesterol measurement have also been produced to help improve accuracy and reliability. Dietitians were the target of a focused outreach effort in FY 1989, because of their central role in the dietary management of patients with high blood cholesterol. A "Dietitian's Kit", based on the guidelines for physicians, was produced in cooperation with the American Dietetic Association and the American Heart Association. FY 1989 was also the first time that National Cholesterol Education Month was observed (in September). In FY 1990, the program will release two major reports--one on population-based approaches to changing dietary patterns and the other on detection and treatment of high blood cholesterol in children and adolescents.

The National High Blood Pressure Education Program (NHBPEP) was established in 1972 to increase awareness among the public and health professionals that elevated blood pressures constitute a serious health risk and that control of blood pressure levels would contribute to a substantial reduction in associated mortality and morbidity. The NHBPEP continues to provide broad programs of professional, patient and public education in partnership with medical, public health and voluntary organizations. An updated report on guidelines for the detection and treatment of high blood pressure received wide dissemination to health care professionals in FY 1989. A major effort in FY 1990 will be a special initiative to reduce stroke mortality in those states in the Southeastern U.S. that have higher stroke rates than the rest of the nation (the stroke belt). The effort involves reporting of state-specific data on the problem; funding of special state-based initiatives in program planning, implementation and evaluation; and intensive mass media efforts in selected markets.

The National Asthma Education Program (NAEP) is the newest of the NHLBI's education programs. It was established in 1989 in recognition of the growing prevalence of asthma in the U.S. and increasing mortality. Its goal is to educate asthma patients, health professionals, and the public about the disease and its management. Modeled after NHLBI's other national education programs, NAEP operates as a partnership with voluntary, professional and community organizations concerned with asthma treatment and control. It will carry out broad programs of patient and professional education, especially efforts aimed at minority populations since they experience higher rates of asthma morbidity and mortality. Program efforts will also be targeted toward schools to help educate school nurses, administrators, and physical education personnel about proper care of students with asthma. In FY 1990, the report of an expert panel will provide recommendations on comprehensive asthma diagnosis, treatment and management for physicians and other health professionals.

In 1987, the NHLBI began the National Blood Resource Education Program (NBREP) in partnership with the three major blood banking organizations in the U.S., as well as other professional and voluntary organizations in the blood area The program aims to help ensure an adequate and safe supply of blood and the appropriate transfusion of blood and blood components. Educational messages are directed at influencing the awareness, knowledge, attitudes, and behavior of health professionals, patients and the general public. In FY 1989, the program released two major reports providing guidance for health professionals in the use of blood products. One report dealt with indications for the use of red blood cells, platelets and fresh frozen plasma, and the other provided recommendations on the use of autologous blood. In addition, a mass media public education program was begun to supplement the efforts of local blood centers in recruiting blood donors. In FY 1990, an important program focus will be the production of a resource kit to help blood banking personnel improve techniques for blood donor recruitment and retention.

The Institute conducts a targeted program on smoking for selected audiences. The program has developed motivational messages and educational tools to aid busy physicians in smoking intervention efforts. The major theme of the materials is taking advantage of clinical opportunities when the patient may be most susceptible to smoking cessation attempts. A series of print and audiovisual products supporting this theme has been produced to stimulate more physician involvement in patient education. In FY 1989, the program successfully collaborated with a state health department, an inner city hospital, and a large health maintenance organization to implement inservice training programs using the clinical opportunities materials. In addition, a comprehensive guidebook based on the clinical opportunities theme was produced for respiratory care therapists. Additional materials, including a poster on relapse entitled "Quit to Win," have received wide distribution. An outreach effort targeting school board members and teachers resulted in distribution of 300,000 copies "Quit to Win" to school districts across the country. The program will continue to work with major public and private sector agencies to assess and disseminate these tools and develop new initiatives. In FY 1989, for example, the program collaborated with the Centers for Disease Control's Office on Smoking and Health to produce a television public service announcement and print materials on smoking relapse and heart disease. In FY 1990, program efforts will be directed to reaching high smoking prevalence populations.

The Institute is planning to begin its sixth education program in FY 1990. The National Heart Attack Early Action Program will focus its efforts to educate health care professionals, their patients, and eventually the public to identify symptoms and signs of early heart attacks and to take immediate actions for treatment. Data from clinical trials suggest that impressive reductions in morbidity and mortality in patients with heart attacks are associated with the use of thrombolytic therapy. Current data also suggest that only a small fraction of patients eligible for thrombolytic therapy are, in fact, receiving such treatment. In 1990, as a first step in developing the program, NHLBI will sponsor a conference to explore various issues related to a national education effort, including the state of current research, public health implications, impact on the medical emergency system, and similar concerns.

Management Savings

The Institute has undertaken several management initiatives, which have led to cost savings, or will make more effective use of available resources. Among these initiatives are procurement reform, which is a part of the larger NIH-wide effort in this area; our position review system; our office automation program; and the reallocation of intramural research resources brought about by the phase out of on-site surgery performed in the Clinical Center.

The overall NIH procurement reform effort, and our part of this program, is changing the way in which individual procurement actions are accomplished and the organizational structure responsible for purchases. The Institute is implementing a plan whereby purchasing agents generally have only procurement duties and, as a result, are able to develop greater expertise in the procurement function. In addition, the procurement agents are usually separated from direct supervision by the programs they serve. This organizational change has been made and it appears that the new system will remain responsive to program needs, while achieving a greater level of compliance with the requirements of the procurement process. Estimated savings from this reform effort are expected to be $429,000 in FY 1990.

The staff of the Institute is one of its most valuable assets. In order to better manage this human resource the Institute started a personnel review process in FY 1989. This review examines every position in the Institute and determines personnel actions that are desirable or necessary.
As a result of this process, division directors, office heads, laboratory chiefs and branch chiefs have an opportunity to discuss how current staff are utilized; review the development of individual staff members; and identify staffing plans and needs. This process has given the senior staff of the Institute an opportunity to participate in the management of a principal Institute resource, improved the planning relative to personnel resources, and has given the Director a sense of priorities regarding the allocation of staff resources, and dealing with other personnel issues.

In order to systematically acquire and promote the use of microcomputer technology in the office environment, the Institute created an Office Automation Systems Branch in July, 1986. The Institute has looked to this branch for help in increasing the productivity of a staff that has the task of managing a growing program without a similar growth in staffing levels. This branch has successfully put in place a five year contract with a minority firm for the acquisition of appropriate hardware and software, and providing assistance to the Institute in applying this technology to the specific tasks the various organizational components need to perform. The most important ongoing task is the development of local area networks for individual organizational units, and then linking these individual networks into a comprehensive NHLBI network system. Four networks with 19 file servers are already in place and linked together. This contract also provides training for staff that is tailored to their functions and the Institute's standard operating procedures, and a hotline to help with individual problems as they occur.

The NHLBI has determined that supporting a full time cardiac surgery unit within the Division of Intramural Research is no longer viable or desirable. Therefore, the Institute has decided to phase out its Surgery Branch and to contract for cardiac surgery with nearby universities, or develop an interagency agreement with the National Naval Medical Center. This decision is based on three major factors: (1) the inability of the Institute to recruit and maintain a permanent cadre of qualified cardiac surgeons; (2) the changing nature of cardiology research, which is evolving from invasive clinical cardiology to new, less invasive or non-invasive molecular biology approaches; and (3) the need to meet program priorities within the relatively stable resources currently available. The Institute anticipates substantial savings from this decision, which will be redirected to rapidly emerging, high priority areas such as gene therapy, cardiac energetics and bone marrow transplantation.

AIDS Research Program

The National Heart, Lung, and Blood Institute (NHLBI) supports research on the acquired immunodeficiency syndrome (AIDS) in two general areas: transfusion transmitted human immunodeficiency virus (HIV) infection; and the hematologic, pulmonary, and cardiac complications of infection with HIV. The 1991 budget request for the AIDS Research Program is $44,463,000, an increase of $2,407,000 over the FY 1990 level of $42,056,000.

Since the identification of HIV, the NHLBI has supported a vigorous research program to protect the safety of the Nation's blood supply. In addition, the Institute has sought to understand the development of the disease in hemophiliacs and other patients who acquire the virus through transfusion of blood and blood products. These NHLBI efforts have contributed to the development of more sensitive tests and more effective screening procedures, and they have served to provide information to physicians regarding good transfusion practices. A recent study has clearly demonstrated that transfusion is becoming safer as a result of these measures.

The Institute seeks to make transfusion even safer by continuing to support the development of more sensitive screening tests for HIV-1 and related retroviruses, improved procedures to discourage persons at high risk of HIV infection from donating blood, and reliable methods to inactivate viruses once they have infected blood and blood products.

NHLBI-supported research on other viruses in the same family as HIV-1, including human T-lymphotropic virus type I (HTLV-I) which has been associated with adult T-cell leukemia/lymphoma, paralysis, and disturbances of the nervous system, has raised additional concerns about the safety of the blood supply. Transfusion can spread HTLV-I and related viruses also.

Respiratory failure due to repeated pulmonary infections is still the most common cause of death in patients with AIDS. A variety of organisms infect the lung, including cytomegalovirus, mycobacterial species, and Pneumocystis carinii. Since 1981, 65,000 cases of pneumocystis have been reported to the Centers for Disease Control, and 40,000 have resulted in death. If projections are correct, more than 150,000 cases can be expected within the next 5 years. Treatment of pneumocystis pneumonia is still unsatisfactory; more than 10 percent of patients die during their first episode of Pneumocystis carinii and more than 40 percent die from a subsequent episode of pneumonia.

In FY 1991, the NHLBI will continue its efforts to define the natural history of lung disease in HIV-infected persons and to assess the effectiveness of various techniques used to diagnose pulmonary infection. Because children and infants represent one of the most rapidly increasing groups of HIV-infected persons, the Institute is supporting research on the pulmonary and cardiac problems that are unique to the pediatric population.

The Institute will expand its efforts to understand the mechanism by which Pneumocystis carinii results in respiratory failure in both children and adults.

The NHLBI is also concerned about HIV-associated heart disease, a common finding in infected persons. As new intervention strategies are developed and AIDS patients survive longer, heart disease may become a more significant problem. For this reason, the NHLBI has funded basic research that will help identify the disease process involved in AIDS-related cardiac complications and suggest possible treatment approaches.

Recent Research Accomplishments

Research to develop more reliable methods of testing donated blood for HIV has yielded promising results. For example, an NHLBI-supported investigator has developed a sensitive and specific HIV antibody test that uses a flow cytometer, an instrument capable of detecting cells that are bound to fluorescent-labeled antibody, to detect the presence of antibody to HIV. In tests of 126 coded blood samples, this method has proved more sensitive and more specific than currently licensed HIV antibody tests.

Another investigator is adapting polymerase chain reaction (PCR) technology for use in the clinical laboratory and blood bank settings. PCR detects the presence of the virus directly, perhaps before antibodies are present, thus shortening the period during which HIV infections are not yet detectable. This investigator has developed an assay that combines the high sensitivity and specificity of PCR testing methods with the technical conveniences of the currently used enzyme immunoassay systems, making it potentially useful to blood banks for pretransfusion screening. In a third project, a simple test to detect antibody to HIV-1 has been developed for use in those parts of the world that lack the sophisticated laboratory equipment necessary to perform currently available tests. This test uses a nitrocellulose dipstick to provide naked-eye evaluations of the degree of surface color intensity. The results are available in 90 minutes and are not dependent on instrumentation.

Several studies have been funded by the NHLBI to assess the current safety of the blood supply by determining the frequency with which HIV-1 infection is transmitted by transfusion of seronegative blood such as blood that tests negative for the virus. For example, the rates of infection with both HIV-1 and HTLV-I have been determined in a group of heavily transfused adults undergoing cardiac surgery who were seronegative for these viruses before surgery. A total of 4,163 patients who had received 36,282 blood components were analyzed. The results showed that the risk of HTLV-I seroconversion (0.024 percent per unit) after receiving blood that was negative for HIV-1 antibody was nearly tenfold greater than the risk of HIV-1 infection (0.003 percent per unit). This study indicates the desirability of screening for HTLV-I. Another study assessed the sensitivity and specificity of tests that detect HIV-1 p24 antigen, a viral protein, and is comparing the results with those of the antibody tests currently used in pretransfusion screening. The result of this study calls into question the need for adding HIV-1 antigen testing to the antibody screening already in use.

Since blood screening procedures are not entirely effective in preventing the transmission of HIV-1, the NHLBI supports the development of procedures that utilize heat or chemicals to inactivate retroviruses in donated blood. These procedures appear to be effective in destroying HIV-1 in blood derivatives such as Factor VIII and Factor IX preparations, but blood components such as cryoprecipitate, which is a source of Factor VIII, red cells, and platelet components, do not tolerate heat treatment. A number of NHLBI-supported investigators have already made important contributions in the development of procedures that inactivate viruses without destroying the effectiveness of the blood product. For example, research on the effectiveness of filtration procedures that remove virus-infected leukocytes from blood and chemical procedures that inactivate HIV-1 shows promise. Several studies have established that more than 99.5 percent of the cell associated virus was removed by filters, and that agents can potentially inactivate the virus. Further studies are underway to determine the safety of these chemicals in blood used for transfusion.

NHLBI supported research on cardiac complications of HIV infection has resulted in several interesting findings. For example, echocardiography, a procedure using ultrasound to look at the heart, showed transient cardiac dysfunction in AIDS patients. Also, HIV has been detected in the cardiac tissue of one patient, but the extent to which HIV infection itself can cause heart disease has yet to be determined. Cytomegalovirus (CMV), which occurs invariably in AIDS patients was found to replicate in the cells lining the blood vessels (endothelium) and in the supporting tissue, but could not replicate in cardiac muscle cells. Some CMV strains produce a diffuse inflammation in the cardiac muscle, whereas other strains cause lesions only in the presence of immunologic suppression.

The Institute's National Blood Resource Education Program (NBREP) was established in 1987 to ensure an adequate supply of blood for the Nation and to ensure that health care providers use blood and blood products only when appropriate. In 1989, the NBREP convened two expert panels. The expert panel on the use of red blood cells, platelets and fresh frozen plasma completed its work and produced a report on this topic for physicians. This report emphasizes that elimination of inappropriate or unnecessary transfusions is an important way to reduce the hazards associated with blood transfusion. The expert panel on the use of autologous blood has also completed its work and produced a report entitled "Transfusion Alert: Use of Autologous Blood", as well as a companion piece for patients entitled, "Your Operation, Your Blood". This material emphasizes the importance of using autologous transfusion whenever possible to eliminate the possibility of transfusion-transmitted disease. The two reports will be disseminated widely to physicians and to blood banking personnel. The report on the indications for the use of red blood cells, platelets, and fresh frozen plasma was published in the FDA Drug Bulletin, which goes to every physician in the U.S.

Within the intramural research program, two recent findings show promise. By inserting the gene for the soluble form of the T-lymphocyte receptor site for HIV (sCD4) into a virus, researchers have developed a vector to transfer this genetic material to other cell lines. This work shows that sCD4 could protect cells from infection by HIV and may lead to a model for gene therapy in the treatment of AIDS. In a separate study, another investigator determined that extracellular levels of glutathione, which is necessary for normal immune functioning, were low in the lungs and blood of persons with HIV infection. This finding could indicate the possible role of glutathione in treatment or prevention of pulmonary opportunistic infections in the lung.

Research Plans

Many basic research questions about HIV-related disease processes in the lung remain unanswered. Further research on lung complications associated with HIV infection will provide greater insight into early disease processes and aid in understanding the events that occur in the transition from healthy to diseased lungs in HIV infected individuals. Pneumonia caused by Pneumocystis carinii is the single most common and well-known complication of HIV infection, but a great deal still needs to be learned about this disease. Despite the availability of reproducible animal models of Pneumocystis carinii pneumonia, the organism and its pathogenic mechanisms are still poorly understood. A FY 1991 initiative will support studies to clarify the nature of lung cell injury caused by Pneumocystis carinii, and help provide important information on mechanisms of selective lung cell injury. A better understanding of interactions between lung cells and Pneumocystis carinii should lead to the development of better therapies for preventing and treating Pneumocystis carinii pneumonia in patients infected with HIV.

Serious conditions characterized by a paucity of various blood cell types, the cytopenias, are frequent findings in persons infected with HIV. Thrombocytopenia, decreased platelets, may cause bleeding complications that can be life-threatening. The NHLBI is currently supporting research on the effects of HIV on bone marrow suppression, one cause of thrombocytopenia. However, thrombocytopenia is principally caused by increased destruction of platelets, a process that is poorly understood. Optimal treatment for this condition also remains undetermined. An initiative will support research to determine how and why this condition develops and the optimal treatment.

Over the past few years, substantial progress has been made in the development of medications specifically directed toward the underlying retroviral infection. Zidovudine (AZT) has been demonstrated to be effective in the treatment of certain groups of patients and is currently approved by the FDA for this purpose. It is becoming clear, however, that use of these medications alone may be restricted by such factors as toxicity and the eventual resistance to the drugs. Several studies have indicated that administration of plasma containing HIV-neutralizing antibody to persons with AIDS can produce beneficial clinical effects. In addition, the presence of neutralizing antibodies in some infected persons appears to be associated with a more favorable prognosis. Based on these data, several investigators have suggested that administration of HIV hyper-immunoglobulin to individuals with AIDS may increase neutralizing antibody levels and prevent progression of disease. Accordingly, a FY 1991 initiative will support research on the use of HIV immunoglobulin as treatment for HIV infection.

The Pulmonary Branch of the NHLBI intramural program will continue to study abnormalities of the lung in individuals with HIV infection. These investigators will further evaluate the phenomenon of decreased lung glutathione levels in persons with HIV infection. This research will include measurement of glutathione levels in the blood and lung of HIV antibody-positive individuals, and will evaluate aerosolized glutathione as a potential agent for augmenting pulmonary extracellular glutathione levels in HIV antibody-positive individuals. The current phase II trial of aerosolized interferon, an agent which has a pivotal role in regulation of immune processes, will continue.

An NHLBI intramural scientist is working to develop agents containing oxygen free radicals that can inactivate enzymes and nucleic acids essential for HIV replication. Preliminary studies have involved the production of DNA capable of binding to a nucleic acid in an HIV gene that is essential for virus replication. This DNA has been found to split the nucleic acid at the target site so that the gene is no longer intact. Research in this area has been limited, however, by the lack of sufficient quantities of HIV-related proteins. Considerable effort is now being devoted to the production of these proteins by recombinant techniques so that this approach might be developed further.

National Heart, Lung, and Blood Institute

Heart and Vascular Diseases

1991 Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$583,135,000	$604,345,000	+$21,210,000

Purpose and Method of Operations

Despite significant reductions in death rates over the past 20 years, cardiovascular diseases continue as the leading cause of death in the United States. The 982,000 deaths due to cardiovascular diseases in 1988 constituted nearly half of all deaths. An examination of the deaths by diagnosis shows a clear dominance of arteriosclerotic-related causes: coronary heart disease, 511,000 deaths; stroke, 150,000 deaths; and peripheral vascular disease, 46,000 deaths. Other cardiovascular diseases, including hypertension, cardiac failure, cardiomyopathies, infections of the heart, and arrhythmia, accounted for an additional 275,000 deaths.

These statistics, although sobering, continue the favorable trend in the reduction of deaths from cardiovascular disease that began in the mid- 1960s. These favorable trends have contrasted with the relatively small reductions in non cardiovascular disease mortality over the same period. Cardiovascular disease caused 55 percent of all deaths in 1962; about 45 percent in 1988. In the 20 years from 1968 to 1988 the overall age-adjusted death rate (all cardiovascular and non cardiovascular causes of death combined) declined from 744 per 100,000 population to 536, a decline of 208 per 100,000 (28 percent). Seventy-seven percent of that decline was in the cardiovascular diseases; 49 percent coronary heart disease; 20 percent stroke; and 8 percent other cardiovascular diseases. Among the various causes of death for which mortality rates have improved in recent years, the decline in mortality for coronary heart disease has had the greatest impact on overall mortality and life expectancy.

Black men and women continue to show marked differences in mortality from stroke and other heart disease compared to white men and women. In 1987, rates of death from stroke between the ages of 35 and 74 were almost twice as high in the black population, and rates for coronary heart disease were twice as high for black women as for white women in the same age group. It is estimated that the mortality rate from smoking is 20 percent higher among blacks than among whites. Given the higher smoking prevalence among some minority groups and their continued high mortality from smoking-related diseases, there is reason to believe that there would be significant health benefits to the Nation to develop and test new smoking cessation strategies for minority populations. The Institute, therefore, has issued a request for applications which sought to develop such strategies with particular attention directed toward the barriers to cessation and positive motivating strategies that are particularly relevant to the selected minority populations.

The total annual cost associated with cardiovascular diseases was estimated at $136 billion in 1987, by far the largest total for any diagnostic group of diseases. The direct costs alone; hospital care, physician and other professional services, drugs, and nursing home care; amounted to $68 billion. It is not possible to separate out from the $68 billion in direct cost the cost of cardiac surgery, but these costs are in the billions. For example in 1988 there were 353,000 coronary bypass operations, which alone must have generated over $9 billion in health care costs assuming each procedure involved about $25,000 in hospital, physician and drug costs. An additional $68 billion was lost to the economy in indirect costs (lost productivity and premature deaths). Coronary heart disease, which kills and disables people in their most productive years, accounted for $56 billion of the 1987 costs associated with cardiovascular disease.

To reduce the economic burden and the mortality and morbidity imposed on the Nation by cardiovascular disease, the Heart and Vascular Diseases Program will continue its emphasis on basic biomedical research, clinical applications of research, clinical trials, and prevention, education, and control programs. Eleven areas are emphasized, each representing a national program category: arteriosclerosis, hypertension, cerebrovascular disease, coronary heart disease, peripheral vascular disease, arrhythmias, heart failure and shock, congenital and rheumatic heart disease, cardiomyopathies and infections of the heart, circulatory assistance, and Acquired Immunodeficiency Syndrome. Within these 11 areas, major emphasis is placed on arteriosclerosis, hypertension, and coronary heart disease programs.

The Heart and Vascular Diseases Program uses several mechanisms to support investigator-initiated and Institute-solicited research. Approximately 75 percent of the funds available to the Heart and Vascular Diseases Program supports research project grants. Research project grants include the individual research project; the program project grant; the first independent investigator research award; and the small business innovation research grant.

Institute-solicited studies allow the Institute to direct research into specific areas that are determined to be of importance to the mission of the Institute. For example, the Heart and Vascular Diseases Program has issued a request for applications to develop and use transgenic animal models to study basic molecular, biochemical, cellular, and physiological mechanisms involved in the pathogenesis of hypertension. Understanding hypertension is greatly complicated by the multifactorial nature of the disease. New experimental techniques and strategies for the development and use of transgenic animals will help remove this major impediment to progress.

Specialized centers of research (SCOR) are very productive confederations of interdisciplinary scientists directing their research at basic and clinical aspects of major disease problem areas including arteriosclerosis and hypertension. The scope of the Specialized Centers of Research in ischemic heart disease has recently been expanded to include coronary and vascular diseases, heart failure, and congenital heart disease. Studies currently supported include the coronary circulation in health and disease, the underlying molecular mechanisms involved in the etiology and pathogenesis of cardiac failure, and the mechanisms involved in the modification or reversal of injury to heart muscle sustained as a result of heart attack.

To assure a sufficient number of specially trained research scientists, the Heart and Vascular Diseases Program continues to support its research career development activities. Included among them are the Research Career Development Award, the Clinical Investigator Award, the Preventive Cardiology Academic Award, the Physician Scientist Award, and the Minority School Faculty Development Award. Each of the mechanisms is designed to attract promising young investigators into the new multi-disciplinary areas of today's biomedical science. For example, the Preventive Cardiology Academic Award, which is made to schools of medicine and osteopathy, is designed to foster the initiation of and improvement in preventive cardiology curricula and to stimulate research careers in the area of primary prevention of cardiovascular disease. In FY 1990, the Institute will seek to encourage investigators from minority medical schools and from medical schools with large numbers of medical students who are underrepresented minorities to apply for the Preventive Cardiology Academic Award.

Academic training for early predoctoral and postdoctoral individuals through the National Research Service Award (NRSA) program has provided trainees with the opportunity to broaden their scientific knowledge and, thereby, extend the potential for qualified researchers to advance in health-related areas. The NRSA training programs have been expanded to include minority institutions through the Minority Institutional Research Training Program and the Research Fellow Program for Investigators at Minority Institutions. The Heart and Vascular Diseases Program currently is supporting an institutional research training program designed to train minority M.D.s over a three-year period to do clinical and basic research in cardiovascular disease with a primary emphasis on special problems of minority populations and, specifically, hypertension in the black population. This program provides the opportunity for investigators to acquire specialized training to meet national research priorities.

Contract supported programs have provided the means to acquire specific research that meets predetermined program needs. For example, the Heart and

Vascular Diseases Program uses research and development contracts to support large scale clinical trials and to support the development and acquisition of treatment devices as in the circulatory assist devices program. Clinical trials provide a critical research step in testing the efficacy of preventive and treatment regimens before they are introduced into practice. As a result of these large scale trials, significant research advances in arteriosclerosis, hypertension, cerebrovascular disease, coronary heart disease, and peripheral vascular disease continue to be realized. An example of a clinical trial supported by the Heart and Vascular Diseases Program is the Systolic Hypertension in the Elderly Program (SHEP). Population-based data show that the prevalence of isolated systolic hypertension (ISH) rises from approximately eight percent in persons age 60-69 to approximately 20 percent in persons over 80. Individuals with ISH are at substantially increased risk for stroke, other cardiovascular disease and death. The primary objective of the SHEP is to determine whether the long-term administration of antihypertensive therapy for the treatment of ISH in elderly persons reduces the combined incidence of fatal and nonfatal stroke.

Rationale for the Budget Request

The FY 1991 budget request for the Heart and Vascular Diseases Program is $604,345,000, an increase of $21,210,000 over the FY 1990 level of $583,135,000.

Atherosclerotic obstruction of arteries is a major cause of heart attack, stroke, and obstructive disease of the peripheral arteries. Recent animal studies have provided important new insights into the influence of aging on the development of arteriosclerosis. According to one well-known hypothesis, the early stages of arteriosclerosis are characterized by a proliferation of smooth muscle cells in the arterial wall at sites of injury to the endothelium lining. The proliferation is stimulated by growth factors such as platelet-derived growth factor and slowed by growth inhibitors such as heparin. Researchers have now found a factor in blood serum that, by reacting with heparin, enables it to reduce smooth muscle cell proliferation. The substance, transforming growth factor beta (TGF beta), is released into blood by platelets during clotting. It has been shown that the smooth muscle cells from the aortas of old animals proliferate more in response to experimental injury to the vessel lining than do those from young animals. It has also been shown that the proliferation of old vascular smooth muscle cells is less dependent on serum or added growth factors than is the proliferation of young ones. Thus aging appears to favor the development of arteriosclerosis by releasing smooth muscle cells from the constraints on proliferation found in the cells of young arteries. Continued research should not only enhance our understanding of the natural development and progression of atherosclerosis with age, but also identify approaches that may provide effective interventions to halt or reverse the atherosclerotic process.

Recently released results of a study of atherosclerotic lesions in sudden death victims provide strong supportive evidence for programs to encourage early adoption of behaviors that reduce cardiovascular risk factors. Postmortem analyses were performed on victims of sudden death who were between the ages of 15 and 34. The coronary arteries and aortas of the victims were examined for gross pathological changes, biochemical data, and arterial topography. The results emphasize how early in childhood the process of atherosclerosis is initiated and how the process produces critical changes in the aorta and coronary arteries in young adults. Over successive age groups, the progression of atherosclerosis was tracked from early fatty streaks to later fibrous plaques. A strong association was also observed between atherosclerotic lesions and cigarette smoking. The findings clearly support the efforts of the American Heart Association and the National Cholesterol Education Program to encourage the adoption of healthy diets in children over the age of two. They also support continued efforts to reduce the incidence of cigarette smoking in the young. Further investigation and analysis will focus upon the relationship of hypertension and diabetes to the development of gross lesions and the early development of atherosclerosis. The additional results should provide information that will aid in the design of programs to control the development of cardiovascular disease.

The early administration of intravenously administered thrombolytic agents for the treatment of acute myocardial infarction represents an important therapeutic advance. Thrombolytic therapy has been shown to recanalize occluded coronary arteries, limit cardiac dysfunction by reducing infarct size, and reduce mortality. Yet early coronary reocclusion remains a problem. It occurs in up to 20 percent of patients and is particularly common among patients with severe residual stenosis. In an effort to prevent recurrent ischemia, it is now common practice to attempt to identify patients at risk for reocclusion by performing coronary arteriography soon after thrombolytic therapy and then, where indicated, percutaneous transluminal coronary angioplasty (PTCA). The Thrombolysis in Myocardial Infarction (TIMI) Phase II Trial was designed to compare an invasive strategy of coronary arteriography 18 to 48 hours after administration of recombinant tissue plasminogen activator (rt-PA) followed by PTCA if indicated with a conservative strategy of performing arteriography and PTCA only in patients with spontaneous or exercise-induced ischemia. When the results of the study were evaluated, they showed that the invasive strategy offered no advantage in terms of reductions in mortality or reinfarction over the conservative strategy. As a result of the study, fewer patients will be exposed to invasive treatments and substantial savings in health care costs should be realized. Continued research should help to refine further the appropriate management of myocardial infarction.

Hypertension, or high blood pressure, is a major risk factor for the most commonly encountered forms of heart and blood vessel diseases. It is the single most important contributing factor to the development of stroke, and it accelerates the development of atherosclerosis in the coronary and peripheral arteries. While it has been apparent for some time that women, at least premenopausal women, have lower hypertension-related disease frequencies than men of comparable age, the reasons for this disparity are not fully understood. However, recently reported results from a comparative study of men and women hypertensives offer some insight into the observed gender differences. One hundred men and women were matched by mean arterial blood pressure, age, race, and body surface area. The women had a higher resting heart rate, higher pulse pressure, and lower resistance in the peripheral blood vessels than men with the same blood pressure. For any level of arterial blood pressure, the total peripheral resistance, and thus the risk of hypertensive cardiovascular disease was lower in women than in men. The conclusion that women are "hemodynamically younger" than men of the same age helps to explain why essential hypertension is less lethal in women. It appears that, at least during the premenopausal years, gender influences not only blood pressure, but also its consequences. Additional research is needed to explore this phenomenon further and to examine the possible causative role of sex hormones.

Hypertension imposes a substantially greater burden upon black Americans. It is not just that the 38 percent prevalence among the black population is significantly greater than the 28 percent prevalence among the white population. Overall, blacks experience a three times greater mortality from hypertensive diseases and among blacks aged thirty-five to sixty-four the hypertensive mortality rate is up to six times greater. Although the etiology of hypertension is not clearly understood, a broad spectrum of potential physiological, psychological, and environmental contributors to the development of hypertension has been identified. Evidence suggests that physiological, behavioral, and environmental factors interact to affect differences in disease prevalence among subgroups and that multifactorial studies of differences among subgroups, such as black and white populations offer the potential for elucidating the etiology of hypertension and its observed higher prevalence among blacks. Findings from a series of investigations on biobehavioral factors in black hypertension have been complex and provocative and have highlighted important differences between blacks and whites in the development of hypertension. Data from these studies indicate that, under conditions of salt loading and stress, hypertensive blacks show exaggerated cardiovascular responses indicative of increased peripheral vascular resistance. In addition, blacks and whites differ with respect to several personality variables, particularly hostility and anger expression, which have been linked in other studies with cardiovascular disease. Black hypertensives also show an increased blood pressure response to infused norepinephrine and an increased heart rate response to isoproterenol under conditions of high salt intake while white hypertensives show decreased blood pressure and heart rate responses under these conditions. These data suggest that a peripheral vascular variation in black hypertension may exist and that it may emerge under conditions of high salt intake. Continued advances in understanding the complex factors that produce a greater hypertension burden among black Americans will allow the development of more effective approaches to reducing it.

Knowledge of the mechanisms by which the brain acts to control cardiovascular function has grown substantially in recent years. Refinements of neuroanatomical methods have allowed the organization of relevant nervous system circuits to be charted and advances in pharmacology have permitted a number of biologically active substances that mediate communication within these circuits to be identified. One important example is provided by our enhanced understanding of the role of neuroactive peptides in the response of blood pressure to stress. The most characteristic response to stress is the release of neurotransmitters, the catecholamines, by the adrenal medulla followed by secretion of glucocorticoids by the adrenal cortex. While the process is controlled by the hypothalamus and the pituitary through the release of adrenocorticotrophic hormone (ACTH), it is mediated during stress by the release of opioid neuropeptides from the anterior pituitary. Evidence now exists that release of opioid neuropeptides is significantly elevated during stress in persons with higher blood pressures. The exaggerated reactivity observed in young adults who are at increased risk for the development of hypertension may be due to alterations in the sensitivity of target cells that respond to these peptides. Further research will help to refine our understanding of the role of opioid neuropeptides and their receptors in the regulation of blood pressure and may lead to new therapeutic approaches for blood pressure control.

Each year, 750,000 patients are admitted to U.S. hospitals with acute myocardial infarction. In addition, many of the more than 500,000 deaths ascribed to coronary heart disease are the result of ventricular fibrillation that occurs in the time between the onset of symptoms of a myocardial infarction and the initiation of medical care. Recent clinical trial results have shown that intravenous thrombolytic therapy can reduce the mortality from heart attacks by between 20 and 50 percent. Moreover, the benefits of thrombolytic therapy are increased as the time between onset of symptoms and administration is decreased. A number of reasons can be identified for delayed administration of thrombolytic therapy, the most intractable of which is patient denial of the symptoms. It is hoped that educational efforts by physicians, nurses, and the media can be effective in reducing the delay due to denial. Current research is addressing another major cause of delay. The Heart and Vascular Disease program is sponsoring a clinical trial to determine whether the delay in initiation of treatment can be reduced by moving the situs of initiation of thrombolytic therapy from the hospital to the ambulance. The first phase of the trial has been successfully completed. It was designed to evaluate the feasibility of having paramedics determine patient eligibility for thrombolytic therapy by radio communication with a hospital-based physician. In the second phase, the safety and efficacy of the approach will be assessed in terms of infarct size, left ventricular ejection fraction, and mortality.

In studies conducted on animals, the drug amiodarone has been shown to have substantial and immediate effects in controlling disturbed heart rhythms during acute myocardial oxygen shortage. Recent studies have now shown that the benefits of amiodarone therapy may also extend to human patients. When intravenous amiodarone was administered to critically ill coronary heart disease patients with life threatening arrhythmias, it was shown to offer substantially improved benefits when compared to conventional antiarrhythmic drugs. Overall, amiodarone administration controlled arrhythmias during the first 24 hours following administration in 50 percent of the patients in the treatment group. In the second 24 hours following administration, the percent controlled increased to 64 percent. Based upon the trial results, it appears that intravenous amiodarone offers an effective therapy for rapid control of spontaneous, refractory, life threatening ventricular arrhythmias in critically ill patients.

Mental stress can cause both symptomatic and asymptomatic myocardial ischemic attacks in patients with coronary heart disease. Impaired heart function, as reflected in significantly reduced left ventricular ejection fraction, accompanies the ischemic attacks. In contrast, the left ventricular ejection fraction remains stable or increases in normal volunteers who are subjected to stress. The silent nature of mental stress-induced abnormalities and their occurrence at lower physiological workloads compared to those evoked by exercise have been confirmed by extended monitoring of heart function during everyday activities. The importance of physical and mental stress in triggering the onset of myocardial infarction and sudden cardiac death is supported by findings that: (1) the frequency of onset of myocardial infarction, sudden cardiac death, and stroke is markedly increased in the period following awakening, (2) the incidence of transient myocardial ischemic events is also increased in the morning hours and the events are frequently preceded by mental or physical stress, (3) a ruptured atherosclerotic plaque underlies most coronary events, and (4) a number of physiologic processes that can lead to either plaque rupture, a hypercoagulable state, or coronary vasoconstriction are accentuated in the morning hours. Further research will help to clarify the role of mental and physical stress and the activities of daily living in precipitating coronary events.

Idiopathic dilated cardiomyopathy (IDC) is a condition in which an abnormally enlarged left ventricle is unable to circulate blood around the body with sufficient force. The usual result of IDC is congestive heart failure. A long list of causes for IDC has been identified, ranging from toxic exposures to mineral deficiencies. In addition, there are now indications that at least some of the patients with IDC may have inherited the condition or at least a predisposition to develop it. In a recent study of 100 patients with IDC, 22 percent were found to have a familial form of the disease. This is significantly higher than previous estimates of its incidence. It is noteworthy that several patients had relatives who did not have the disease, but did have enlarged ventricles. It is thought that those family members with enlarged hearts may be carriers of an IDC-related gene or have a genetic marker for the IDC-related gene. The suggestion of a significant genetic basis for IDC indicates that future research should focus upon genetic factors and the interaction of genetic and environmental factors that may predispose to the development of the disease. Long term follow-up of patients should greatly improve our understanding of the natural history of IDC.

Not much more than a decade ago, the function of the vascular endothelium was considered to be limited to keeping most of the plasma proteins from escaping and presenting a hemocompatible surface to prevent blood from clotting. In the past few years, however, an impressive number of activities have been documented in which the vascular endothelial cells engage. In particular, it is now known that the endothelium is importantly involved in the process of vasoregulation. Endothelin is a recently identified protein secreted by endothelial cells that has been shown to cause constriction of the blood vessels and is thought to play a significant role in the control of blood pressure. It has been shown that endothelin produces increased arterial blood pressure by causing increases in the resistance of peripheral blood vessels and that the increased resistance of the peripheral blood vessels is associated with increased resistance in blood vessels of the heart and decreased cardiac output. As blood flow and the rate of filtration in the kidneys are markedly reduced, salt retention results. It is speculated that endothelin may counter the effects of blood vessel relaxing factors. Continued research on endothelin will clarify its role in the development of hypertension.

In spite of the dramatic improvement in the clinical results in cardiac transplantation associated with the introduction of the immunosuppressant, cyclosporine A, transplant rejection remains a significant problem. In the early period after transplantation, rejection is the leading cause of death. However, recent studies using OKT3 monoclonal antibodies are showing considerable promise as an immunological intervention to prevent rejection. OKT3 monoclonal antibodies are directed against OKT3 antigen that is found on all circulating human T cells, including those responsible for transplant rejection. The splenic cells used to produce the hybridoma cells are taken from mice that have been immunized with T-lymphocytes isolated from human blood. To have a significant impact on clinical results in heart transplantation, any new immunosuppressive agent must meet three fundamental criteria. First, it must have a powerful and specific inhibitory effect on helper/inducer T cell function. Second, its mechanism of action should be distinct from currently used immunosuppressants. Finally, it must have nonoverlapping toxicities with currently used immunosuppressants. OKT3 monoclonal antibodies meet these criteria. Recent investigations have shown that monoclonal antibodies have the potential to move transplantation forward rapidly. They are not only successful in reversing refractory cases of rejection but also very effective as prophylaxis to prevent rejection. In addition, when monoclonal antibodies are used, the dosages of other immunosuppressants can be reduced, thereby reducing the incidence of toxic side effects. As a class of reagents for immunosuppressive therapy, monoclonal antibodies offer significant prospects for improved transplant outcomes.

Lipoprotein (a), denoted Lp(a), is a class of cholesterol containing particles in the blood that are similar to LDL. The gene for Lp(a) is inherited in a dominant fashion, and elevated levels of circulating Lp(a) are associated with an increased risk of cardiovascular disease. Recent research results suggest that Lp(a) may also be a powerful predictor of vein graft stenosis following coronary artery bypass surgery. A stepwise increase in mean Lp(a) levels in serum has been found in groups of patients with increasing vein graft blockage. The ability to assess the risk of vein graft stenosis in patients undergoing bypass surgery and to predict cardiovascular disease in general may be enhanced by newly developed assays that are sensitive to Lp(a) but insensitive to its closely related serum component, plasminogen. Continued research on Lp(a) will refine further our understanding of its role in the development and progression of cardiovascular disease.

The areas of research described above will continue to be supported by the Institute and will permit progress toward the continued decline in death rates from cardiovascular diseases.

National Heart, Lung, and Blood Institute

Lung Diseases

1991 Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$175,836,000	$186,699,000	+$10,863,000

Purpose and Method of Operations

Respiratory diseases are among the leading causes of death and disability in the United States. About one in every five persons in this country reports some chronic respiratory problem, and chronic obstructive pulmonary diseases are the fastest rising among the leading causes of death. When the mortality from chronic obstructive pulmonary disease (COPD) is combined with bronchitis, bronchiectasis, emphysema, and asthma, these conditions accounted for 82,000 deaths in 1988. COPD and allied conditions now rank fifth among the 10 leading causes of death in the United States. Of increasing concern is the 54 percent increase in death rate for COPD over the last 20 years in contrast to declines in mortality for most other major causes.

Lung cancer death rates in recent years show similar trends; there has been a much greater increase for women than for men. Increased cigarette smoking among women appears to be a cause of the rising mortality from both lung cancer and COPD. In contrast, the death rates for disorders associated with infant respiratory distress syndrome have declined rapidly over the same period. Still, respiratory diseases, excluding lung cancer, caused an estimated 194,000 deaths in 1988.

Respiratory diseases account for more bed days, work-loss days and physician office visits than any other major disease group. Chronic obstructive pulmonary disease and asthma are especially prevalent, with as many as 24 million persons estimated for 1988. Of the 9.9 million persons with asthma, 8.7 million were under age 65. Chronic bronchitis affects an estimated 11.9 million persons of all ages, the majority of whom are in the work force. Many other respiratory problems, including disorders of pulmonary circulation, interstitial lung disease, pneumoconiosis, and neonatal pulmonary disorders, add to the overall picture of 2.2 million hospital admissions and 16 million days of hospital care in 1987 due to lung diseases.

In 1987, lung diseases cost the nation's economy an estimated $36 billion in direct health expenditures ($12 billion), together with indirect costs of morbidity ($24 billion) and mortality ($7 billion). Direct costs measure expenditures on lung diseases for hospital care, physicians' services, and drugs. Indirect mortality costs reflect lost potential productivity, measured in lost future wages by those who died of lung disease prematurely, before normal life expectancy. Thus, pulmonary diseases have cost our Nation greatly both in human suffering and in dollars. Although many of these diseases, once they occur, are chronic and incurable, many are preventable. Improved prevention and management of chronic pulmonary diseases provide a difficult and exciting challenge.

The broad mission of the Lung Diseases Program is to combat these problems by providing more effective diagnosis, treatment, and prevention of pulmonary disease. A multifaceted approach is employed that emphasizes improved understanding of the causes of disease, greater knowledge of pathogenesis, and improved techniques for early diagnosis and more effective management. Nine areas are emphasized of which seven are National Program categories: structure and function of the respiratory system (including lung development, lung cell biology, and pulmonary physiology); chronic obstructive pulmonary diseases (emphysema, chronic bronchitis, and asthma); pediatric pulmonary diseases (neonatal respiratory distress syndrome, bronchopulmonary dysplasia, cystic fibrosis, and bronchiolitis); occupational and immunologic lung diseases (pulmonary fibrosis); pulmonary vascular diseases (pulmonary edema, hypertension, and thromboembolism); respiratory failure and Acquired Immunodeficiency Syndrome. In addition research on prevention, education, and control of lung disease and research training and career development are supported in each of the National Program categories.

The Lung Diseases Program uses several mechanisms to support investigator initiated and Institute solicited research. Approximately 67 percent of the program's budget supports research project grants; 165 percent supports research centers; 13 percent supports career development programs, training, and other grant research; and 4 percent supports research contracts. Research project grants include the traditional investigator initiated research project, which is the major source of fundamental research contributing to our understanding of normal lung function and the processes involved in respiratory disorders, and leading to improvements in the diagnosis and management of pulmonary diseases.

The Lung Diseases Program augments its research portfolio by publishing Institute initiated requests for applications in selected areas of science. These special solicitations are designed to encourage exploration of problems that are not being addressed or are being insufficiently addressed by investigator initiated grants. For example, the Lung Diseases Program has recently issued a request for applications on beta-adrenergic modulation of airway function. The request is intended to stimulate cellular and molecular biologic approaches to delineate the mechanisms regulating beta-adrenergic function in normal airways and its perturbation in disease.

Center grants support a spectrum of activities with a multi- disciplinary focus on a specific disease entity or biomedical problem and are developed in response to an announcement to fulfill a specific programmatic need. The Lung Diseases Program currently supports specialized centers of research in respiratory diseases of neonates and children, chronic diseases of the airways, occupational and immunologic lung diseases, pulmonary vascular diseases, adult respiratory failure, cystic fibrosis, and sleep apnea.

To meet the needs for research training and career development in the pulmonary field, the program supports a variety of career development awards, and individual and institutional training awards. The National Research Service Awards (NRSA) includes individuals at the pre- and post-doctoral level, senior fellows who wish to acquire new research capabilities, and medical students who wish to acquire research training during off-quarter or summer periods. In the career development area, the Clinical Investigator Award, the Physician Scientist Award, and the Research Career Development Award are the main mechanisms of support. The recently initiated Preventive Pulmonary Academic Award encourages the development and improvement of teaching of prevention of respiratory diseases in both undergraduate and graduate medical training and research in methods for the prevention of lung diseases.

Research and development contracts are another mechanism available to develop and apply new knowledge or to test, screen, or evaluate a product, material, or device for use by the scientific community. Contracts are often the mechanism of choice for large-scale trials or other clinical studies, where the parameters and methodology are specified with considerable detail. The Lung Diseases Program is currently supporting a registry of patients with severe congenital deficiency of alpha-1-antitrypsin. Twenty-two clinical centers and a data and coordinating center are participating. The objective of the registry is to characterize the clinical and laboratory course of severe congenital alpha-1-antitrypsin deficiency whether or not the patient is undergoing long-term replacement therapy. Patient recruitment began April 1, 1989 and during the first six months 236 serum samples were submitted to the central laboratory for phenotyping and measurement of alpha-1-antitrypsin levels. Approximately 90 percent of the patients tested are being found eligible for enrollment.

Rationale for the Budget Request

The FY 1991 budget request for the Lung Diseases Program is $186,699,000, an increase of $10,863,000 from the FY 1990 level of $175,836,000.

The recent discovery of the gene that causes cystic fibrosis, the most common fatal inherited disease among Caucasians, offers great promise for an enhanced understanding of the disease. There are now opportunities for not only identifying the basic biochemical defect underlying the disease but also for determining how it causes the pulmonary pathology that is the usual cause of death from cystic fibrosis. While there are a number of variations of the cystic fibrosis defect and additional mutations remain to be identified, it is now known that the most common cystic fibrosis defect involves the loss of a single amino acid. The protein produced by the cystic fibrosis gene shows structural similarities to a number of membrane localized transport systems. Using a combination of cell biology and genetic approaches, scientists are studying the function of the gene product in pulmonary cells and the mechanisms by which this defective protein causes the abnormal ion movement, viscous mucus, and pulmonary infections characteristic of cystic fibrosis. Identification of the cystic fibrosis gene has also made feasible the development of an animal model for the disease. Absence of an animal model has inhibited study of the disease processes as well as development of new and more effective treatments.

Research on the genetic and biochemical abnormalities underlying cystic fibrosis-associated lung problems has been hampered by a limited availability of cells and tissues from the airways and lungs of cystic fibrosis patients. This difficulty may soon be alleviated, however, as a result of recent advances in the culture and transformation of human airway epithelial cells. New techniques have enabled production of cystic fibrosis cell lines having unlimited growth potential and continued expression of the cystic fibrosis gene defect. Using gene transfer techniques, viral DNA containing the immortalization function has been introduced into cystic fibrosis airway epithelial cells grown in cell culture. The cystic fibrosis cell lines produced by this method are capable of propagating indefinitely and faithfully expressing what appears to be a fundamental abnormality of airway epithelium in cystic fibrosis. Like airway epithelial cells of cystic fibrosis patients, the cell lines exhibit increased transport of sodium ions across the cell membrane but are impervious to chloride ions.

While new approaches to treatment are likely to arise from our increased understanding of the pathogenesis of cystic fibrosis and the discovery of the cystic fibrosis gene, other efforts have already led to the development of a potentially effective new treatment. The promising new therapy relies upon the aerosolized diuretic compound, amiloride, which inhibits excessive salt and water absorption from cystic fibrosis airway secretions. Preliminary results obtained in adult patients indicate the ability of amiloride to "normalize" the flow properties of sputum and to slow the disease-induced decline in pulmonary function of CF patients. These findings, if confirmed, should lead to rapid efforts to assess the protective effects of the drug in younger patients. In addition, alternative modes of delivery for the drug are being assessed to determine whether they improve its efficacy.

The more than 12 million workers in the United States employed in agricultural industries are at increased risk for developing lung disease due to their exposure to a variety of complex organic substances. Diseases such as farmer's lung and occupational asthma have been well documented and studied in agricultural workers. Recent studies suggest that a newly recognized group of respiratory diseases that have not been identified with any known allergens may also pose a significant health risk to agricultural workers. A trend in agriculture toward indoor production of farm products appears to be linked with an increased incidence of this class of airway diseases that are characterized by chronic cough, difficulty in breathing, and bronchial spasms. The available evidence indicates that the increased incidence of these chronic diseases is due to the higher concentrations of pollutants to which workers are exposed as they move indoors. In agricultural confinement workers such as livestock breeders, abnormalities in lung function have been linked to specific classes of contaminants that are present in the indoor environment. For example, lowered lung capacity has been shown to be associated with increased exposure to organic dusts and organic material while bronchial spasms have been associated with increased airborne microbial contaminants. Although washings from the airways of affected workers indicated damage to the airway lining and showed inflammatory processes to be prominent, the asthma mediator, histamine, did not appear to be involved nor was there any specific response to known occupational allergens. Further work will be required to identify the causative agents and to characterize the disease process so that effective preventative approaches can be developed and implemented.

Although heart-lung transplantation has been performed successfully since 1981, the peri-operative mortality is still about 12 percent and one- and three-year survivals are approximately 70 and 55 percent, respectively. Major factors contributing to the mortality associated with lung transplants include the lung's susceptibility to infection, its tendency for immunologic rejection, and chronic lung failure due to obstructive airway disease. Now, however, new methods are being developed that will enable earlier detection of lung infections and rejection. The new methods include cytological examination of circulating lymphocytes, measurement of interleukin-II receptors, and detection of the expression by killer cells of a gene for the production of serine protease. Each of these methods offers the advantage of providing information indicative of early stages of systemic viral infection and of rejection without requiring a lung biopsy.

Recently, neural mechanisms have been shown to play a significant role in the pathogenesis of asthma. For example, neuropeptides released from sensory nerves are capable of causing constriction of the airways, edema, and increased mucus secretion. A newly discovered enzyme, neutral endopeptidase (NEP), that was found in the airways appears to play a major role in regulating the activity of a group of neuropeptides called tachykinins. The rate of degradation of the tachykinins is regulated by NEP. NEP is present in the airways in many different kinds of cells and tissues. It normally functions by cleaving neuropeptides near their sites of release or action, thus limiting their physiological action. Inhibition of NEP activity has been shown to increase the magnitude of secretory, constrictor, vascular permeability, and cough responses to neuropeptide stimulating agents. Further studies of NEP are crucial to improving our understanding of asthma and all other inflammatory diseases where the tachykinins play an important role.

While asthma is only slightly more prevalent in blacks than in whites, the rates of hospitalization and mortality for asthma are more than twice as high in blacks than in whites. Although the specific reasons for these disparities are not known, it is known that blacks in general have less access to health care. Moreover, many inner city minority residents do not have access to a continuing source of health care and so they use emergency rooms for the treatment of chronic conditions like asthma. Introduction of effective asthma education programs to inner city families with asthmatic children may help to reduce the health care burden due to asthma. While several evaluations of asthma education programs have shown that the frequency and severity of attacks can be reduced, none of the programs were evaluated in very young children, despite the fact that asthma is usually diagnosed before the age of two. However, a study is currently being conducted in a black and Hispanic population in New York City that targets the parents of children who have been hospitalized for asthma. The parents attend a three session educational program to learn about prevention and symptom recognition and how symptoms can be effectively controlled at home so that future emergency room visits and hospitalizations can be avoided. The study, which will be completed in 1992, will provide information on the factors associated with hospitalization for asthma in this population and will provide a model intervention to teach management of asthma to parents at an early stage in its natural history.

The primary risk factor for emphysema and other forms of chronic obstructive pulmonary disease (COPD) is cigarette smoking. By studying individuals with a rare, inherited form of emphysema caused by a severe deficiency of alpha-1-antitrypsin, scientists have learned about the mechanisms underlying the far more common form of emphysema caused by cigarette smoking. The irreversible structural damage to alveolar walls that characterizes emphysema is thought to result from an imbalance between elastase, an enzyme which breaks down lung tissue, and alpha-1-antitrypsin, a serum protein which inactivates elastase. Yet, verification of this theory and other studies of the basic and clinical aspects of alpha-1-antitrypsin deficiency have been hampered in the past by the absence of an appropriate animal model. Now, however, as a result of an NHLBI-initiated program, a transgenic mouse has been developed that expresses the human alpha-1-antitrypsin deficiency. This new mouse model displays many of the physical and histologic changes seen in humans and should provide an important new tool for advancing emphysema research. Emphysema research has been further advanced by the recent report that in some smokers large numbers of neutrophils accumulate in the capillaries of their lungs immediately after smoking. Since neutrophils are thought to be the main source of elastase, it is possible that in some smokers lung tissue is destroyed when a localized excess of elastase is released by accumulated neutrophils. Further research may show this to be a critical causative mechanism in the development of emphysema in smokers.

Neonatal respiratory distress syndrome (RDS) continues to be a major cause of morbidity and mortality in premature infants. The condition is caused by the inability of the lungs of premature infants to make surfactant, a material that helps the lungs to inflate easily and that prevents their collapse during expiration. Investigators have examined the expression of surfactant proteins in the lungs of infants who died from RDS. The lungs of the most premature infants exhibited none to minimal staining for three of the surfactant proteins. Although the lungs of infants who died from RDS at later gestational ages showed progressively increasing amounts of surfactant proteins, the intensity of the immunostaining for the surfactant proteins never reached the levels found in lung tissue from infants who died at a comparable age but from other causes. These results confirm previous findings of an association between RDS and low levels of the major surfactant protein (SP-A) in amniotic fluid and underscore the important role of it in enhancing surfactant function. The availability of molecular probes for the proteins should make it possible to learn more about the factors controlling their expression in the developing lung. Exploration of the mechanisms that control the synthesis of surfactant proteins should provide explanations of the surfactant protein deficiencies that underlie the persistent respiratory distress and mortality experienced by some infants.

Individuals who suffer from the sleep apnea syndrome spend a large portion of the night with severely reduced blood oxygen levels due to an inadequate airflow. The recent application of magnetic resonance imaging (MRI) and ultra fast X-ray computed tomography (cine CT) to visualize the anatomy of the upper airway is providing important diagnostic information about the anatomy of the upper airway in sleep apnea. For example, it is now possible to determine whether a problem is due to collapse in a specific anatomical site or is instead the result of a more generalized multi-focal abnormality. It has been shown that a portion of the oropharyngeal region of the upper airway is a common site of collapse. The narrowing in this area appears to be related to a thickening of the walls with an increased fat disposition. It has also been shown that this region of the airway partially occludes in sleep apnea patients even when they are awake. Findings such as these have a direct bearing on treatment options, since diffuse involvement indicates the likely failure of any localized surgical procedures. Further work with advanced imaging techniques should result in improved methods for determining the most effective therapeutic approaches to alleviating upper airway obstruction in patients with sleep apnea syndrome.

These areas of research will continue to provide valuable information about lung diseases and will aid in the development of new therapeutic strategies for individuals afflicted with lung diseases.

National Heart, Lung, and Blood Institute

Blood Diseases and Resources

1991 Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$177,329,000	$177,534,000	+$205,000

Purpose and Method of Operations

For decades, the illnesses, deaths, and health care costs resulting from blood disorders were incompletely reported, and the quantities and costs of blood collected, processed, and transfused were not reported at all. Now research has revealed the widespread involvement of blood disorders in death and disability; for example, the role of thrombosis in the pathology of many disorders.

The acquired diseases in which abnormalities of the blood are prominent, such as coronary and cerebral thrombosis, phlebitis, and other thromboembolic conditions, affect millions of Americans. In 1988, blood diseases were reported as the primary or underlying cause of 295,000 deaths in the United States. In 1987, the estimated economic costs (expenditures for hospital care, professional services, nursing home care, drugs, and medical sundries, productivity lost through illness or death) amounted to $43 billion.

Some blood diseases are also chronic disorders. The genetic blood diseases such as hemophilia, sickle cell anemia, Cooley's anemia, and G-6-PD deficiency have lifelong effects on several million Americans. In the aggregate, they are the primary cause of death in as many as a thousand patients per year. Their chronic effects, however, range from mild to life-threatening and from transitory to continuous, and they result in major morbidity and cost for the health care system.

There are almost two dozen blood products transfused to patients. They range from whole blood to individual proteins separated from plasma. In 1987, 13.2 million units of whole blood were collected in the United States and about 4.0 million patients received either whole blood or components derived from the donated units. Over the last decade and a half, there was a trend away from the transfusion of whole blood (5 million units in 1971; approximately 1 million in 1987) in favor of component therapy. The use of red cells, platelets, plasma, and cryoprecipitate increased significantly over the period 1971-1987.

Adverse effects of transfusion remain a problem. The recipients of whole blood, its components, derivatives, and substitutes occasionally experience transfusion reactions. The most frequent is hepatitis, and the most severe is AIDS, both of which are major concerns of the Institute. The incidence of transfusion-transmitted hepatitis in multiply transfused patients who have received whole blood or red cells is at least three percent and possibly as high as five percent. Over 90 percent of the cases are caused by non-A, non-B hepatitis virus, with the rest caused primarily by infection with the B hepatitis virus. Out of the approximately 4.0 million individuals who were transfused with whole blood or red cells, the estimated incidence of transfusion-transmitted hepatitis ranges between 120,000 to 200,000 recipients.

To address these issues, the Blood Diseases and Resources Program is organized into five National Program areas: thrombosis and hemostasis, which includes thromboembolic, platelet, and hemorrhagic disorders; red blood cell disorders, such as the thalassemias and aplastic anemia; sickle cell disease; blood resources, which includes blood component and derivative therapy, safety of blood therapy, immunohematology, transplantation, blood substitutes, and blood resource management; and Acquired Immunodeficiency Syndrome. The major programmatic responsibilities of these areas are to reduce the morbidity and mortality caused by blood diseases by developing programs which will lead to their prevention and treatment, and ensure the availability of adequate supplies of safe and efficacious blood products that are appropriately transfused. In pursuit of this mission the scientific community is encouraged to participate in the full range of investigative opportunities available in basic research, clinical research, clinical trials, applied and developmental research, and demonstration and education research. It is also encouraged to assist the emerging disciplines and specialized areas of medicine in developing, upgrading, and organizing their activities in ways that create a climate favorable for productive research and conducive to mature, sophisticated investigation. The Institute is also committed to assuring an adequate number of outstanding investigators by providing specialized training and development opportunities.

The Blood Diseases and Resources Program uses several mechanisms to support investigator initiated and Institute-solicited research. Approximately 66 percent of the program's budget supports research project grants; 14 percent supports research centers; 7 percent supports career development, training, and other grant research; and 13 percent supports research contracts. Research project grants include traditional individual research projects, which are the major source of fundamental research contributing to our understanding and management of blood diseases and blood related disorders.

As needs arise, the Blood Diseases and Resources Program publishes requests for applications in specific areas of science. These solicitations are designed to encourage exploration of problems requiring special research efforts. For example, the Blood Diseases and Resources Program has recently issued a request for applications to stimulate basic and clinical research to clarify the role of cellular, humoral, and vascular factors of blood coagulation in the pathophysiology of sickle cell disease and to define new therapeutic strategies that might help to limit or reverse the process of vaso-occlusion. Another example is the request for applications to encourage basic research on the biochemical mechanisms that result in fibrinolysis and thrombolysis with particular emphasis on the thromboselectivity of plasminogen activators and their regulation of plasminogen activator inhibitors.

Career development awards, such as the Transfusion Medicine Academic Award, encourage medical schools to develop curricula in cooperation with blood centers to foster the career development of aspiring scientists with outstanding potential to become independent researchers or teacher-investigators. The transfusion medicine curriculum also has been adapted for use for nurses so as to improve the quality of nursing care and research in transfusion medicine. Two more competitions will be supported before this program terminates. To date, 28 medical schools and schools of veterinary medicine have been supported. Special announcements, such as the Research Career Awards in Thrombosis encourage investigators to train for research in thrombosis. A number of new awards that span high school through post-doctoral levels seek to strengthen the training of minority individuals and institutions for biomedical research.

The Blood Diseases and Resources Program supports two kinds of centers: Specialized Centers of Research (SCORs) and Comprehensive Centers. The Blood Diseases and Resources Program currently supports SCOR programs in thrombosis and transfusion medicine that encompass both basic and clinical research. The ten Comprehensive Sickle Cell Centers emphasize a comprehensive team approach to care. New collaborative clinical research studies have been initiated by the centers in the areas of transfusion therapy, pain management, and the diagnosis and monitoring of clinical events using magnetic resonance imaging.

Research and development contracts are another mechanism available to develop and apply new knowledge or to test, screen, or evaluate a product, material, device, or component for use by the scientific community. Contracts are often the mechanism of choice for large-scale clinical trials or other clinical studies, where the parameters and methodology are specified with considerable detail. The Blood Diseases and Resources Program has recently awarded six research contracts to establish epidemiologic studies of human retroviruses in blood donors from areas of the country that are reportedly at high, medium, or low risk for HIV. This comprehensive study will assess the need for donor screening and the potential impact on the blood supply, identify risk factors for retrovirus infection with the donor population, and monitor changes in risk over time. An important objective of this program is to obtain data on the demographic and epidemiologic characteristics of participating donors. This program includes provisions for a coordinating centers with central data management and central facilities for testing and serum storage. Each center is expected to obtain 25,000 samples per year for a total project period of five years.

Rationale for the Budget Request

The FY 1991 budget request for the Blood Diseases and Resources Program is $177,534,000, an increase of $205,000 over the FY 1990 level of $177,329,000.

Although the prevailing view in the 1970s was that patients with sickle cell disease rarely survived beyond the age of 30, the expected life span and the likely cause of death of patients with sickle cell disease remain as major unresolved issues. The Cooperative Study of Sickle Cell Disease (CSSCD), which has followed over 4,500 patients prospectively for the past ten years, has provided a unique opportunity to learn more about the mortality associated with sickle cell disease. Four hundred patients over the age of 35 were enrolled in the study, many of whom were in their fourth and fifth decades. Prospective data on deaths in 73 patients under the age of 20 confirmed that the highest mortality occurs between ages one and three and that infection is the major cause of death. After age ten, trauma and cerebrovascular complications became the leading cause of death. Analysis of clinical events showed little evidence of specific risk factors for death except in patients with cerebrovascular events. Low hemoglobin levels and low levels of fetal hemoglobin were associated with an increased risk of death. The study indicates that 89 percent of patients with hemoglobinopathies can live at least to age 20, a figure far greater than the 50 percent previously reported. This finding of improved overall survival provides increased optimism for patients and families with sickle cell disease. It is believed that the improvement is due, at least in part, to early parental education and counseling, to programs of comprehensive care, and, more recently, to the prophylactic use of penicillin in infants. More precise determination of the cause of death in cases of sickle cell disease will be possible by a centralized pathology unit that can correlate longitudinal clinical and pathological data.

Splenic sequestration is a major cause of acute deaths in sickle cell patients between the ages of six months and two years. It is characterized by rapid enlargement of the spleen, acute anemia, and progressive circulatory collapse. Because it can progress to death in a matter of hours, it requires prompt diagnosis and management. Based upon the Cooperative Study of Sickle Cell Disease, there is reason to believe that the overall mortality from this complication has decreased. Only one death due to splenic sequestration has occurred during the course of the study. Early identification of infants with sickle cell disease and parental education programs that teach mothers about the syndrome and about how to palpate for enlarging spleens have undoubtedly contributed to the reduction in mortality. However, the report of an eight week old infant with splenic sequestration indicates a continued need for parental attention. Since this case was the youngest so far reported with splenic sequestration, it would probably have been unsuspected had the child not previously been diagnosed with sickle cell disease. In fact, this case was diagnosed because a newborn screening program was established in the state of the child's residence in response to the mandate of the NIH Consensus Development Conference on Newborn Screening for Sickle Cell Disease.

Factor VIII, the trace plasma glycoprotein that plays a central role in normal blood clotting and is missing or defective in patients with hemophilia A, has been produced by recombinant DNA technology. It is currently undergoing its first clinical trial among hemophiliacs. The recombinant product has been shown to be identical to the currently used plasma derived product in both structure and function and preliminary data from the clinical trial indicate that it also has a half life similar to the plasma derived product. After one year, the efficacy of the recombinant product has been clearly established. A larger multicenter study is now underway that is using a second generation recombinant Factor VIII. Preliminary data from this second trial indicate that the second generation product is also fully compatible with the plasma-derived product. The success of these trials highlights the potential of recombinant Factor VIII as a safe and efficacious form of replacement therapy. It is projected that recombinant Factor VIII will be clinically available in 1991. Mortality will be reduced when the recombinant product is generally available since it will be free of the viral contaminants that have been a leading cause of mortality and morbidity in both infants and adults.

Treatment of hemophilia A by replacement therapy for Factor VIII is frequently complicated by the development of neutralizing antibodies against Factor VIII. A therapeutic strategy for patients with neutralizing antibodies against Factor VIII that circumvents the need for Factor VIII has recently been made possible by the development of recombinant Factor VII. Factor VII, in combination with its accessory protein, tissue factor, initiates clot formation by an alternate pathway known as the extrinsic pathway of coagulation. Factor VIII does not participate in the extrinsic pathway to any great extent. Human recombinant Factor VII has been administered to dogs with hemophilia A to determine its ability to correct the hemostatic defect. Hemophilia A dogs lacking Factor VIII demonstrated an immediate increase in plasma recombinant Factor VII and prompt normalization of the bleeding time. Recombinant Factor VII was also effective in correcting the hemostatic defect in dogs with hemophilia B which is characterized by a lack of Factor IX. By demonstrating that Factor VII is an effective form of therapy in dogs with hemophilia A and B, these studies indicate the potential for recombinant Factor VII to treat hemophilia in humans.

Bone marrow transplantation is an effective and accepted therapy for an increasing number of diseases of the bone marrow and the immune system. Bone marrow transplants differ from most tissue or organ transplants in that bone marrow contains immunocompetent cells. Not only can the graft fail, but also the graft can reject the recipient in what is known as graft-vs-host disease. Hence, matching for tissue types must be more stringent than with other kinds of organ and tissue transplantation. Until recently, most marrow donors were siblings, carefully matched for HLA (tissue) antigens. However, since only a small proportion of candidates for bone marrow transplants have matched siblings, additional family members were tried first as donors and then followed by unrelated, HLA-matched community volunteers. Among patients stratified by disease and other risk factors, the results of transplanting marrow from matched community volunteers, half-mismatched relatives (parents), and matched siblings are about equally successful. The National Marrow Donor Registry is a fully functional, computerized file of individuals who have been HLA-typed and agreed to participate as potential bone marrow donors. The number of listed donors has more than doubled in the past year and is now over 60,000. In excess of 200 transplants have been performed using donors from the Registry. In addition to conducting and supporting the research necessary to make bone marrow transplants standard therapy, the Institute will provide for professional and public education to speed its movement from successful experimental therapy to widespread general use.

Current estimates place the incidence of post-transfusion non-A,non-B (NANB) hepatitis at between three and five percent of transfusions, making it by far the most common viral complication following transfusion. The development of methods to inactivate or remove virus from blood and blood components would greatly reduce the morbidity and mortality associated with transfusions. Recently, investigators have reported a promising method to inactivate hepatitis viruses in blood derivatives. It is known that substances containing constituents of a class of plants called psoralen can produce a light induced toxicity. Plasma samples containing various concentrations of either NANB or hepatitis B virus (HBV) were treated with psoralen compounds and exposed to long wavelength ultraviolet light. Chimpanzees were used to evaluate the potential for photochemicals to destroy viruses in factor VIII concentrates while retaining clotting factor activity. These experiments showed that significant quantities of HBV and NANB virus were inactivated by photochemical decontamination. Furthermore, factor VIII concentrates retained most of their biological activity following photochemical treatment. It appears that psoralen compounds bind to viral nucleic acid and, in the presence of ultraviolet light, effectively inhibit replication of the virus. Investigators have yet to assess the effects of photochemical decontamination on cellular blood components, but there are grounds for optimism since it is known that the method is not disruptive to cell membranes and has the potential to inactivate a wide range of viral agents in cellular blood products, including whole blood, packed red cells, and platelet concentrates.

Protein S is a vitamin K-dependent plasma protein which functions as a necessary cofactor in the regulation of the coagulation cascade. Patients with protein S deficiency have a predisposition to thrombotic disease. Both hereditary and acquired forms of protein S deficiency have been described. Protein S is synthesized by the liver and by cells lining blood vessels throughout the body. It circulates in two forms: (1) free protein and (2) complexed to another regulatory protein, c4b binding protein. Only free protein S is biologically active. The human gene for this protein, which is located on chromosome 3, has been cloned. The genetic lesion responsible for defective protein S function has recently been identified in three protein S deficient families with hereditary thrombophilia. It appears that a single base mutation in the protein S gene gives rise to a mutant form of the protein which is unable to bind to its regulatory protein. The deficiency arises because mutant proteins are recognized as defective and cleared from the bloodstream. Therapy with recombinant protein S is expected to reduce the incidence of morbidity and mortality in infants at risk for hereditary protein S deficiency.

The Blood Diseases and Resources Program administers a major portion of the Institute's AIDS research program. Several of these programmatic activities are described in the AIDS research program narrative.

These areas of research will continue to contribute to improving the safety and adequacy of the nation's blood supply and will help accelerate the resolution of pressing research issues in blood diseases.

National Heart, Lung, and Blood Institute

Intramural Research

1991 Authorization: Indefinite.

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
412	$85,127,000	424	$92,621,000	+12	+$7,494,000

Purpose and Method of Operations

The Institute's intramural research program conducts basic and clinical research related to diseases of the heart, blood vessels, lung and blood. Over 200 scientists in nine research laboratories and eight clinical branches conduct approximately 240 independent research projects. In FY 1989, about 1,715 Clinical Center patients were studied under 80 clinical research protocols. In addition, 4,897 ambulatory patients participated in research projects through the Ambulatory Care Research Facility.

The combination of basic laboratory research and clinical investigation conducted in close proximity to one another facilitates communication and an exchange of ideas among scientists and stimulates the formation of multidisciplinary research teams to address specific research problems. This interaction permits basic research results to be quickly directed into clinical studies and clinical researchers to identify areas where basic research is needed. Among the diseases studied in this environment are blood diseases such as sickle cell and aplastic anemia; cardiac diseases such as coronary atherosclerosis and hypertension; and pulmonary diseases such as emphysema. Areas of major research that involve collaboration between basic and clinical research include the continued development of gene therapy technology and, for the first time, use of gene transfer in the development of treatment of diseases in patients; the application of magnetic resonance imaging technology in patients to improve our understanding of how the heart functions and of metabolic changes that occur in disease states; the biology of experimental and clinical arteriosclerosis and its manifestations; the pathophysiology of hypertensive vascular diseases; and the therapeutic effect of exogenous alpha-1-antitrypsin on familial emphysema. In addition to the independent research conducted by Institute investigators, collaboration with scientists in other NIH institutes, other government agencies, universities, private companies, and with scientists in other countries contributes to an effective research program.

Several laboratories are conducting studies of biological phenomena at the cellular and molecular level that may increase our knowledge of normal cellular activity in heart and blood vessels, lung, and blood and changes that occur in pathologic conditions. The Laboratory of Biochemistry conducts basic research on enzymes, metabolic regulation and protein chemistry. Investigators in the Laboratory of Cellular Metabolism examine the enzymes responsible for mediating the effects of hormones and the influence of drugs on their cellular function. The Laboratory of Chemical Pharmacology studies the mechanisms by which drugs and their metabolites exert their effects. The Laboratory of Chemistry isolates and studies the structure and properties of biologically important compounds such as peptide hormones. The Laboratory of Cell Biology seeks to understand the molecular processes that underlie muscle contraction, cell movement, and the movement of organelles within cells. The Laboratory of Biochemical Genetics conducts basic research in neurotransmission, and basic mechanisms that regulate the expression of genes during cell differentiation.

One laboratory, the Laboratory of Technical Development, develops instrumentation and related methodology to assist in the application of recent advances in technology and pathophysiology to the diseased heart and lung. The laboratory has made state of the art advances in the clinical application of spectroscopy, thermal tipped catheters, chromatography, and the appropriate use of mechanical pulmonary ventilation.

The Pulmonary Branch studies diseases of the alveolar structures in the lung where gases are exchanged between air and blood. The laboratory continues to evaluate the treatment that it developed for familial emphysema, conducts basic research on fibrotic lung disorders, and is beginning several new studies on the often fatal opportunistic infections in the lungs of AIDS patients.

The research projects of the Molecular Hematology Branch and the Clinical Hematology Branch focus on genetic blood diseases. The Clinical Hematology Branch seeks new treatments for thalassemia, sickle cell anemia, aplastic anemia, and various syndromes of bone marrow failure. The Molecular Hematology Branch conducts research on the mechanism of gene transfer and the basic molecular mechanisms of gene expression and protein synthesis using hemoglobin as a model system.

The research projects in eight laboratories and branches relate to diseases of the heart and blood vessels. The Hypertension-Endocrine Branch conducts research on the causes of and therapy for hypertension with particular emphasis on the neurohumoral and vasoactive systems that control circulation. The Cardiology Branch studies the pathophysiology of and treatments for coronary heart disease, angina pectoris, and hypertrophic cardiomyopathy. The Laboratory of Kidney and Electrolyte Metabolism investigates water and solute transport in cells and the mechanisms that control this transport. The Laboratory of Molecular Cardiology studies the molecular mechanisms regulating the interaction of major contractile proteins present in smooth, skeletal, and cardiac muscle. The Molecular Diseases Branch seeks to understand the molecular and structural properties of apolipoproteins, the physiological role of apolipoproteins and lipoproteins in lipid transport, and the mechanisms involved in the regulation of cellular metabolism and transport of lipids. The Pathology Branch investigations relate to coronary, valvular, and congenital heart disease with a recent emphasis on the evaluation of mechanical and bioprosthetic cardiac valves.

The Institute's newest laboratory, the Laboratory of Cardiac Energetics, is moving forward with the acquisition and installation of a unique high field, magnetic resonance instrument. The machine will permit human studies on the biochemistry, function, and micro-anatomy of the human heart that are not possible on standard low field instruments. This instrument will permit new investigations, which will add to the accomplishments that these investigators have had in their in vitro and animal research. For example, data from research already performed indicate that the utilization of metabolic substrates, such as fats and sugars, and the delivery of oxygen are the major regulatory steps of cardiac energy utilization. They have also shown that pharmacological modification of substrate utilization by the heart in vitro can modify cardiac performance. This may lead to a new class of drugs for the treatment of heart disease. Data to date indicate that these types of studies hold great promise in the investigation of the physiology and pathology of the human heart and other vital organs. In addition, these studies have the advantage of being non-invasive and being immediately applicable to clinical research. The investigators, in conjunction with the NIH Clinical Center, will continually evaluate the new instrument for its potential use as a diagnostic tool for a wide variety of clinical conditions.

Rationale for the Budget Request

The FY 1991 budget request for the intramural research program is $92,621,000, an increase of $7,494,000 over the FY 1990 level of $85,127,000. These funds will continue the research activities of the intramural research program. Brief descriptions and program highlights from these many activities are described in the following material.

A major advance toward the development of successful human genetic therapy was taken in FY 1989 with the conduct of the first clinical studies of human gene transfer. The study was designed to allow researchers to monitor the ability of cultured tumor-killing white cells to attack and shrink tumors. A marker gene was inserted into human lymphocytes taken from the tumors of patients with advanced malignant melanoma. The cells were then re-administered to the patients. Although the genetically-engineered cells have no enhanced therapeutic potential, the ability of scientists to track the fate of the cells may lead to improved protocols for adoptive immunotherapy in cancer patients.

Elevated levels of high density lipoproteins (HDL) are associated with a reduced risk of premature cardiovascular disease, while reduced levels of HDL are associated with an increased risk. Both the liver and the intestine have been proposed as major sites of synthesis for apoA-I and apoA-II, the two major apolipoproteins in HDL. Lipoproteins that contain only apoA-I, called LpA-I particles, appear to be particularly effective in protecting against cardiovascular disease. Recent work has indicated that, while the liver produces both apoA-I and apoA-II, the intestine synthesizes only apoA-I. This suggests that the intestine may be an important source of the protective LpA-I particles. The factors that modulate the biosynthesis of intestinal LpA-I particles will be an active area of research in the future.

Endothelium regulates vascular tone by secreting substances that modulate the activity of surrounding vascular smooth muscle. Acute and chronic hypertension impair endothelium-mediated vasodilators in experimental animals. To determine whether patients with hypertension also manifest an endothelium-dependent abnormality in vascular relaxation, the forearm vascular response to acetylcholine (Ach), an endothelium-dependent vasodilator, and to nitroprusside, an endothelium-independent vasodilator, was compared in hypertensive patients and normal subjects. The vasodilator response to nitroprusside was similar in the two groups, whereas the response to Ach was attenuated in the hypertensive patients. It is speculated that the impaired endothelium-mediated dilation in hypertensives may exacerbate or even causally contribute to the hypertensive process.

Oxygen radical-mediated oxidation of proteins, lipids, and nucleic acids is implicated in a number of pathological processes, including adult respiratory distress syndrome, atherosclerosis, reperfusion-ischemic damage, and hypertension. That tissue damage during ischemia-reperfusion is due to oxygen-free radicals is becoming increasingly apparent. In recent animal studies, two markers of oxygen-radical damage were observed following ischemia-reperfusion. While the presence of the two markers during ischemia suggests that some of the damage occurred prior to reperfusion, most of the observed damage occurred in the 15 to 60 minutes following reperfusion. There is animal evidence that oxygen radical mediated damage can be limited by administration of bacterial endotoxin. In the absence of endotoxin treatment, rats are highly sensitive to oxygen toxicity. Yet, after a single injection of endotoxin, rats withstood 15 days of 100 percent oxygen without manifesting any signs or markers of lung injury.

In order to achieve effective genetic therapy for such hemoglobin disorders as sickle cell disease and severe beta thalassemia, it is necessary first to introduce a globin gene into bone marrow hematopoietic stem cells and then to achieve specific high level expression of the transferred gene in red cell precursors. Retroviral mediated gene transfer is the most efficient method of gene transfer available. While an appropriately designed retroviral vector is capable of infecting approximately one in ten mouse hematopoietic stem cells, the transferred human globin genes have been expressed in mouse red cells at a very low level. Assays devised to explore systematically the effects of hematopoietic growth factors on survival and proliferation of hematopoietic stem cells and progenitor cells in vitro have shown that interleukin-3 (IL-3) is absolutely required to support mouse stem cells in vitro. The repopulating potential of bone marrow cultured for 4 to 6 days in the presence of IL-3 is ten times greater than bone marrow cultured without the growth factor. Interleukin-6 (IL-6) has been found to be ineffective alone, but it does augment the effectiveness of IL-3. Since work in primates indicates that findings in the mouse system can be directly extended to higher animals, it follows that IL-3 and IL-6 are important components of any culture medium designed to sustain stem cells during retroviral-mediated gene transfer.

Coronary heart disease patients who develop refractory ischemic symptoms and are not candidates for initial or repeat bypass surgery pose a major therapeutic problem. One approach that is being explored is to use extracardiac blood vessels to supply the heart through newly developed collateral connections. The effectiveness of the internal mammary artery (IMA) in providing collateral flow has been evaluated in animal experiments with surgically induced chronic ischemia. When the IMA was implanted in the ischemic zone created by restricting the flow in the left anterior descending coronary artery, collateral circulation from the IMA developed over eight weeks was shown to provide 20 percent of the circulation to the ischemic area. The circumflex coronary artery was responsible for another 30 percent of the collateral flow. Subsequent simultaneous occlusion of both the IMA and the circumflex coronary artery caused systolic dysfunction in the affected area, while occlusion of either one alone produced no effect. Thus the flow provided by the IMA and the newly formed collateral circulation offer a potentially effective therapeutic approach for refractory ischemia.

Sarcoidosis is a nonmalignant, chronic, systemic disorder which can involve almost any organ, including the heart. It is characterized by an inflammatory process that is associated with granuloma formation in affected organs. Although the etiology of sarcoidosis is unknown, it is recognized that T-cells play a critical role in its pathogenesis. Individuals with active sarcoidosis have accumulations in their lungs of helper/inducer T-lymphocytes. The T-cells accumulation in the lungs is due, at least in part, to processes in the lung that stimulate their activation and proliferation. Recent efforts to gain an understanding of the reasons for the accumulation of T-cells have provided evidence to support the hypothesis that accumulation in the lung in pulmonary sarcoidosis is a response to persistent and specific antigenic stimulation. Further research of this kind is essential if the pathogenesis of sarcoidosis is to be fully explained.

Chronic myocardial toxicity is produced by a certain family of antineoplastic agents. One drug in the family, doxorubicin, has been shown to produce a dose-dependent dilated cardiomyopathy that is characterized clinically by congestive heart failure. A new animal model of doxorubicin induced chronic myocardial toxicity has recently been developed from spontaneously hypertensive rats. The new rat strain is much more sensitive to the development of chronic cardiotoxicity than closely matched normotensive rats. Thus, the new animal model is in accord with evidence that systemic hypertension may be a risk factor for the development of doxorubicin cardiomyopathy in humans. The drug, ICRF-187 has been shown to decrease considerably the chronic toxicity of doxorubicin in both the spontaneously hypertensive rats and the genetically matched normotensive rats. The new model will aid in identification of additional agents to inhibit doxorubicin toxicity since the effects of analogs of ICRF-187 on doxorubicin toxicity can now be evaluated in an animal model.

Arteries from hypertensive patients and arteries from spontaneously hypertensive rats both show a greater mass of smooth muscle cells than vessels from corresponding normotensive controls. When rat vascular smooth muscle cells were studied in culture, the rate of proliferation of smooth muscle cells from spontaneously hypertensive rats was found to be greater than for normotensive rats. New evidence indicates, however, that some existing antihypertensive drugs may inhibit smooth muscle cell proliferation. Such antihypertensive drugs as hydralazine, nifedipine, and verapamil have been shown to inhibit DNA synthesis in smooth muscle cells from spontaneously hypertensive and normotensive rats. Other antihypertensive agents, such as nifedipine and verapamil have been shown to stimulate DNA synthesis slightly in both rat strains. These findings suggest additional therapeutic potential for existing antihypertensive agents. For example, myocardial hypertrophy can be reversed in spontaneously hypertensive rats by doses of verapamil that do not significantly reduce blood pressure.

The above areas of research will continue to be supported by the NHLBI. These studies and other basic and clinical research projects supported by the intramural program will continue to provide valuable information about heart, blood vessel, lung, and blood diseases and will aid in the development of new therapeutic strategies for individuals affected by these diseases.

National Heart, Lung, and Blood Institute

Research Management and Support

1991 Authorization: Indefinite.

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
422	$48,596,000	431	$51,303,000	+9	+$2,707,000

Purpose and Method of Operations

Research Management and Support provides funds for the overall management of the Institute's programs; and for managing research grant, research training, and research contract portfolios. In addition, this activity provides funds for the Office of Prevention, Education, and Control, which conducts a variety of activities aimed at reducing the risk of heart and lung disease, and informing health professionals and the public about blood donation and appropriate use of blood and blood products.

The Office of the Director plans, directs, coordinates and evaluates the Institute programs. Three staff offices help carry out this management function. The Office of Program Planning and Evaluation collects and analyzes data for use in developing, planning and evaluating Institute programs and advises the Director on program plans and policies. The Office of Administrative Management provides financial management, personnel management, procurement, and management analysis services, and advises the Director on equal opportunity activities and special programs to increase minority participation in heart, lung, and blood research. The Office of International Programs coordinates international cooperative research activities in the areas of cardiovascular, respiratory, and blood diseases, which provide an opportunity for American scientists to cooperate with colleagues throughout the world in projects of high national priority, mutual interest and benefit.

Five divisions manage the extramural award programs of the Institute. The Division of Extramural Affairs provides initial scientific merit review of program project and center grants, facilitates the activities of the National Heart, Lung, and Blood Advisory Council, and provides stewardship of federal funds through proper grant and contract management. The Division of Heart and Vascular Diseases, the Division of Lung Diseases, the Division of Blood Diseases and Resources, and the Division of Epidemiology and Clinical Applications manage research grant, research training and research contract supported programs within their respective areas of expertise. The Division of Epidemiology and Clinical Applications also conducts the Framingham Heart Study and the Honolulu Heart Program.

The Office of Prevention, Education, and Control develops and coordinates the Institute's professional and public information and education policies and programs on heart and vascular, lung and blood disease, and blood resources. This Office administers the National High Blood Pressure Education Program, the National Cholesterol Education Program, the NHLBI Smoking Education Program, and the National Blood Resource Education Program.

Rationale for the Budget Request

The FY 1991 budget request for research management and support is $51,303,000. These funds permit the continuation of national education programs developed and coordinated by the Institute; the continuation of the Honolulu Heart Program and the Framingham Heart Study; and the continuation of program oversight and evaluation functions. These funds also permit the development of new programs and initiatives in high priority areas.

One of the areas that has high priority is the implementation of several programs aimed at increasing the numbers of underrepresented minorities who wish to pursue research careers. The Minority Access to Research Careers summer training program is an example of a recent initiative in this area. The Institute is also interested in pursuing research and developing intervention strategies for those diseases that affect minorities in disproportionate numbers. For example, special education efforts targeted to minority groups is part of the Institute's ongoing intervention strategy.

In FY 1991, the Institute is planning to add its fifth national education program tentatively called the National Heart Attack Early Action Program (NHAEAP). Securing immediate treatment for a heart attack and thereby salvaging valuable heart tissue is critical for reducing morbidity and mortality. Recent advances in therapy, especially from clinical trials evaluating thrombolytic therapy, suggest that impressive reductions in morbidity and mortality in heart attack patients are associated with the use of such therapy. In addition, many of the estimated 300,000 sudden deaths, which are largely the result of ischemia-induced ventricular fibrillation, could be prevented, given proper medical attention. As such, a national program to educate health care professionals, their patients, and, eventually, the public to identify symptoms and signs of heart attacks and to take immediate action for treatment is now possible and indeed, necessary.

The NHAEAP will be implemented in the following stages: Stage I (FY 1990): plan program, conduct initial workshop to refine issues, and establish databases; Stage II (FY 1991): refine and review program plan, initiate program, and direct educational efforts to emergency medical systems personnel and community health professionals; Stage III: direct educational efforts to high risk patients and their families; Stage IV: if warranted, direct educational efforts to public.

Prior to the FY 1991 program initiation, efforts will be directed toward establishing a program base that is sound scientifically, educationally, and economically. The first stage of the program (FY 1990) establishes various databases which will direct subsequent stages of the program as well as the program evaluation. A conference will then consider the issues delineated by these various analyses and discussions with experts in the field. Subsequent stages of the program will be directed toward educational activities using various mechanisms and organizations.

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Detail of Permanent Positions

	1989 Actual	1990 Appropriation	1991 Estimate
ES-60	12	13	13
ES-61	9	10	10
Subtotal	21	23	23
GS/GM-15	44	45	45
GS/GM-14	72	74	74
GS/GM-13	55	55	58
GS-12	44	45	46
GS-11	55	57	59
GS-10	5	7	7
GS-09	52	55	58
GS-08	26	27	27
GS-07	112	115	115
GS-06	48	50	50
GS-05	19	22	24
GS-04	11	15	17
GS-03	3	6	6
GS-02	3	5	5
Subtotal	549	578	591
Grades Established by act of July 1, 1944 (42 U. S. C. 207):			
Assistant Surgeon General	1	1	1
Medical Director	29	29	29
Director Grade	5	5	5
Senior Grade	17	19	19
Subtotal	52	54	54
Ungraded	17	22	22
Total permanent positions	639	677	690

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

New Positions Requested

	Grade	1991 Number	1991 Annual Salary
Intramural Research			
Research Chemist	GS-13	1	$44,092
Research Biologist	GS-13	1	44,092
Microbiologist	GS-11	2	61,874
Biologist	GS-09	2	51,138
Histopathology Technician	GS-09	1	25,569
Biological Lab Technician	GS-05	2	33,750
Clerk-Typist	GS-04	2	30,166
		11	290,681
Research Management and Support			
Public Health Educator	GS-13	1	44,092
Nutritionist	GS-12	1	37,079
		2	81,171

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

Advisory and Assistance Services

The Institute procures the services of experts and consultants to participate in conferences and workshops. The purpose of these meetings is to assess the state of science in selected areas of research, to develop recommendations regarding research strategies that will enhance the chances of success, and develop ideas about how to stimulate new research in areas that are important but languishing. Institute staff, or for that matter any one person, cannot be omniscient in every aspect of complex areas of research. Therefore, the Institute solicits outside advice as an aid to its decisions regarding program directions and the most effective use of limited resources. Each year the Director reviews the plans for conferences and workshop, and allocates funds to each Institute component in an amount that will permit that component to pursue those conferences and workshops that have the highest priority. Obligations against these allocations are tracked in monthly reports on budget status. For individual experts and consultants, the Institute is requesting an increase of $40,000 for FY 1990 over that obligated in FY 1989 and $42,000 for FY 1991 over FY 1990. This request will permit the Institute to maintain its individual experts and consultants at a current services level based on FY 1989 obligations.

For management and professional support services, the Institute is requesting an increase of $318,000 for FY 1990 over FY 1989 obligations, and an increase of $13,000 for FY 1991 over FY 1990. The increase from FY 1989 to FY 1990 appears inordinately large because one contract had large unobligated balances in FY 1989, which permitted the Institute to continue this contract without additional funds. This procurement action is undergoing a competitive renewal action, which is anticipated to more accurately reflect past programmatic levels. The increase for FY 1988 to FY 1990 is $114,000. This contract permits the Institute to prepare a number of background documents used at the conferences and workshops described above, as well as background materials used in Congressionally mandated reports and other documents used to described the Institute's programs. This contract also provides logistic support services for various meeting and conferences that help the Institute carry out its mission. The Director, NHLBI reviews and approves the documentation related to this contract, and reviews each year the planned activities that this contract supports. The Director allocates a specific amount for this contract each year.

The amount for personnel appointments permits the Institute to hire an expert or two to assist the accomplishment of specific tasks. For example, the Institute hired an AIDS coordinator on an expert appointment to assist in pulling together various components of its AIDS program into a cohesive whole.

TUESDAY, MARCH 13, 1990.

NATIONAL INSTITUTE OF DENTAL RESEARCH

WITNESSES

DR. HARALD LÖE, DIRECTOR
DR. WILLIAM F. RAUB, ACTING DIRECTOR, NIH
DR. PRESTON A. LITTLETON, JR., DEPUTY DIRECTOR, NIDR
DR. LOIS COHEN, DIRECTOR, EXTRAMURAL PROGRAM, NIDR
DR. ABNER L. NOTKINS, DIRECTOR, INTRAMURAL RESEARCH PROGRAM, NIDR
EARLENE S. TAYLOR, BUDGET OFFICER, NIDR
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

OPENING REMARKS

Mr. NATCHER. At this time, we take up the budget request for the National Institute of Dental Research for fiscal year 1991.

We have before the committee Dr. Löe, the Director of the National Institute of Dental Research.

Dr. Löe, it's a pleasure to have you back before our committee, and before you give us your statement, tell us who you have with you there at the table, Doctor.

Dr. LÖE. Thank you, Mr. Chairman. With me today are Dr. Abner Notkins, Director of the Intramural Research Program; Dr. Lois Cohen, Director of the Extramural Program; Dr. Preston A. Littleton, Deputy Director; and Mrs. Earlene Taylor, Budget Officer of the Institute.

Mr. NATCHER. Thank you very much, Doctor.

Now, at this time, we would be pleased to hear from you.

Dr. LÖE. Mr. Chairman, last year I reported a dramatic improvement in the dental and oral health of America's children and the young adults of this country.

I also said that the reduction of the diseases in these groups amounted to a savings in the Nation's dental bill of approximately $3 to $4 billion a year. That was the good news.

The bad news was that older Americans are not doing well at all, that approximately 50 percent of aged Americans had lost all their teeth, and that those who still had teeth experienced the most tooth decay and the most severe periodontal diseases.

ORAL HEALTH INITIATIVES

Our initiatives for the 1990's will be to capitalize on the successes that we have had in the young and decisively address the problems of the aged.

Our goals are to eliminate toothlessness in America and to put an end to the pain and the misery from oral disease among our senior citizens. We intend to find out who is most at risk, whether for reasons of health or because of such factors as lack of health care access or education, and come to their aid with the best we can in the way of treatments and prevention.

Our other initiative relates to the so-called special care patients. These are people of any age whose oral health is compromised because of systemic diseases and systemic treatments. They include children with genetic and congenital disorders like cleft palate, the most common birth defect of the face and the mouth. And those affected by ectodermal dysplasias in which components of the skin fail to develop properly and teeth are either misshapen or missing. And people with osteogenesis and dentinogenesis imperfecta which leads to brittle bones and brittle teeth.

Other special care patients suffer from autoimmune disease like Sjögren's syndrome associated with dry eyes and dry mouth, or scleroderma in which the skin hardens and shrinks so much that these people have difficulty in opening their mouth.

A third group are patients with diseases that predispose to oral problems. These include people with diabetes, AIDS, and various sorts of blood disorders.

The last group I will mention are people who regularly take any of the 400 or more prescription drugs or over-the-counter medications that affect the salivary glands, as well as patients who are being, or have been, treated for cancer by radiation or chemotherapy, both of which can have devastating effects on the oral cavity.

Mr. Chairman, with these initiatives, I am trying to underscore the obvious, that the mouth is connected to the rest of the body and that the mouth, in significant ways, is a mirror of general health and general disease.

For too long people have thought of the NIDR as a one- or at best a two-disease Institute. That is a great misconception.

It's true that our Institute is special in that we deal with the problems that affect all 250 million Americans. We are showing what we can do with tooth decay and periodontal diseases in mainstream American. As we broaden the scope and broaden our mission, and with your support, Mr. Chairman, we look forward to showing you what we can do for the millions of special care and high risk groups addressed in these initiatives.

Our request for 1991 is $140,520,000. I shall be happy to answer any questions that you may have.

[The statement and biography of Dr. Harold Löe follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute of Dental Research

Mr. Chairman, the National Institute of Dental Research is beginning the decade of the 1990's with a new Long-Range Research Plan that will take us to the year 2000. The new plan, available later this Spring, establishes two major initiatives that have become high priorities for the Institute.

The first initiative reflects our concern for "special care" patients. These are people whose oral health is affected by systemic diseases or systemic treatments. We are talking about Americans with such well-known conditions as diabetes, cystic fibrosis, lupus, and AIDS, as well as patients with rare or so-called "orphan" diseases such as scleroderma, a disease in which skin and connective tissue harden and shrink, leading to limited mouth opening; osteogenesis and dentinogenesis imperfecta, in which bones and teeth are poorly developed and subject to fracture; the ectodermal dysplasias, in which essential components of skin and teeth fail to develop properly; and Sjögren's syndrome, a condition of dry eyes and dry mouth, often complicated by arthritis, that primarily affects women. Sjögren's syndrome may not be so rare, since recent estimates suggest that up to 2 million Americans may be affected.

We would also include among special care patients individuals who have suffered oral complications because of cancer chemotherapy or radiation to the head or neck. In addition we intend to expand research on a number of primary oral conditions that merit increased attention such as oral cancers, certain chronic facial pain conditions, and disorders of taste and smell.

All told, special care patients add up to millions of Americans. We have been alerted to their needs because the patients and their families themselves have formed organizations to address those needs and because their health problems are increasingly coming under research attack by NIDR-supported scientists. Indeed, we foresee a time when dentists in America may be the primary point of entry into the health care system for many people, providing diagnosis as well as treatments or referrals for many of these conditions.

I can illustrate that broadening of the scope of the dentist with an account of what happened recently during a visit by a Congressman to a dental clinic affiliated with one of the country's leading dental schools. The delegation had stopped to observe a dental examination in progress in which the dentist had noted a spot on the tongue of the patient. Later, the Dean of the dental school, who had also observed the patient, confided that while positive test results would be needed to confirm the diagnosis, the patient almost certainly had Kaposi's sarcoma and that this sign may well have been the first indication that the patient, a young man, was infected with the AIDS virus.

The AIDS epidemic is a good example of the extent to which oral health research has expanded to include the full range of diseases and disorders that affect the oral tissues. In our new Long-Range Research Plan we use the phrase "from AIDS to Xerostomia" (the technical term for dry mouth) to express this broadened capability. Recent indicators of our progress include:

- The development of an animal model for osteogenesis imperfecta and isolation of the genes for major bone growth factors involved in bone and joint diseases. These studies may lead to the use of specific growth factors to reverse the connective tissue damage that is seen, for example, in osteoarthritis.

- Use of the drug pilocarpine to treat Sjögren's syndrome and other conditions of dry mouth in which some functioning salivary gland tissue remains. Researchers are studying the basic defect in Sjögren's syndrome, noting changes in saliva and the presence of circulating antibodies that are directed against the body's own tissues as markers of disease activity.

- Development of sensitive tests indicating that human papilloma virus (HPV) is present in a very high percentage of cancers affecting the lining and floor of the mouth, and the tongue, larynx, and pharynx of patients. This association will be followed up with analyses of how the virus may interact with other factors, such as tobacco use, in causing oral cancer.

- Clinical studies of the use of permanent dental implants instead of removable dentures in young patients with congenital absence of teeth (as seen in cases of ectodermal dysplasia) as well as in older patients who have lost all their teeth.

- Development of experimental models of chronic pain due to nerve injury (neuropathy). An unexpected finding was considerable spontaneous nerve activity in the damaged nerves. This could account for the heightened sensitivity and severity of pain experienced by patients with diabetic neuropathy and other forms of neuropathy.

In terms of progress in AIDS research, I would add:

- Continued evidence that oral signs and symptoms may be the first indications of infection with HIV. The fungal disease, candidiasis, appears to be the most prevalent oral condition associated with HIV infection, followed by "hairy leukoplakia," a lesion seen most frequently on the tongue. Because hairy leukoplakia is considered predictive of frank AIDS, investigators are increasing efforts to determine its cause and develop means of early diagnosis, treatment, and prevention.

- Issuance of a Request for Applications to explore the role of saliva in HIV infection. We hope to award several grants to expand on earlier studies indicating that saliva probably plays little or no role in the transmission of HIV, and may, in fact, contain a factor that inhibits the infectivity of the virus.

- Refinements in transgenic mouse models of HIV. In collaboration with the National Institute of Allergy and Infectious Diseases, NIDR scientists have inserted individual HIV genes in mice so that models are available for the study of juvenile AIDS, fetal abortion, and HIV-associated kidney disease.

- Expanded collaboration with the Walter Reed Army Institute of Research in a natural history of oral manifestations of HIV infection in military personnel. The new research activities include developing treatments for oral conditions and studies of the severe periodontal disease seen in some patients.

Our second major initiative for the nineties is one we have discussed in previous hearings before this Committee. The Research and Action Program for Improving the Oral Health of Adults and Older Americans was developed in response to findings from recent NIDR nationwide surveys of oral health. Our adult survey established that Americans 65 and older have the most severe oral health problems of any age group, with rates of toothlessness better than 40 percent and with extensive caries and periodontal diseases among those who still have teeth. We have defined the goals of the Research and Action Program to be the elimination of toothlessness among future generations of Americans and the prevention of further deterioration of the oral health of individuals with already compromised dentition--with a target date for accomplishment set for the next 20 years. NIDR will pursue basic and clinical research on normal age-related changes in the oral tissues as well as changes due to oral and systemic disease and treatments. "Action research" will involve NIDR in the transfer of laboratory findings to public and professional use through clinical trials, demonstration research, and similar efforts. Much of the research effort will focus on the prevention and treatment of dental caries and the periodontal diseases since these are the major causes of tooth loss. Thus by giving the program high priority we are expressing the need to finish the job of eliminating the two diseases that have for so long dominated dentistry.

In the past year we have worked closely with the Centers for Disease Control, which will assume responsibility for working with state and local health agencies in implementing oral health promotion and disease prevention activities. In addition, we have gained the enthusiastic support of other government agencies, including the Indian Health Service and the Health Resources and Services Administration. The Assistant Secretary for Health has now requested that the Program be identified as a Public Health Service-wide activity involving a chartered interagency task force. We believe that such a focus will greatly facilitate a coordination and collaboration that will eventually involve the dental professional community, the private sector, community leaders, and consumer groups.

The Research and Action Program is emphasizing the importance of identifying individuals of any age who are at risk for oral health problems for whatever reason--dental, medical, or socioeconomic. Thus the program complements the Special Care Patient initiative but adds demographic factors such as age, education and income in determining risk. We are especially mindful of the need to improve the oral health of racial and ethnic minorities. Past surveys have been limited in sampling and analytic techniques, often reporting data for Whites and "non-Whites" or "Blacks and others." Even within the limited compass of these surveys, however, it is clear that racial and ethnic minorities generally fail to match the level of oral and general health attained by the average American. Further, if interventions designed to prevent disease and promote health are to be effective, they must take into consideration cultural values, language, financial means, access to services, and other variables affecting health care. Last May we invited a distinguished group of Black, Hispanic, and Native American health professionals to discuss health issues and ways to resolve them. We have incorporated their ideas in our new research plan and have increased efforts to enhance recruitment of racial and ethnic minorities into oral health research.

We have held similar meetings with representatives of private industry and oral health researchers from other countries. The intent of these meetings was to define areas which could benefit from collaboration, not only to facilitate the conduct of research and research training, but to broaden the base for support in ways that could benefit all parties. One outcome of these meetings has been the decision to form a liaison group made up of grantees, private sector representatives, and NIDR staff which would meet periodically to discuss ongoing research with the potential for collaboration. NIDR is committed to such approaches as ways to assure that America maintains its leadership and competitive edge in biomedical research worldwide.

We have also incorporated into our research plan a variety of support mechanisms that have already proven their worth in dental research. These include the continued use of research centers and other large grant mechanisms as recommended by an external advisory group reporting to this Committee in 1985. At present we are supporting 19 research centers. This will be increased to 21 later this year with the award of the two new clinical core research centers that were made possible through the support of Congress. Core centers will be especially valuable to academic institutions eager to enhance their research potential.

The need to ensure an adequate pool of research investigators also dictates our continued emphasis on research training and career development awards. In particular, the 5-year Dentist-Scientist Award has been extremely successful and we are graduating our first class this June. We have reached our "steady state" goal of having approximately 125 candidates enrolled in the system at any one time and, from the qualities of the candidates we are seeing, feel confident that these young men and women will make major contributions to dental research and education throughout their careers. Through them, their mentors, and other leading oral health research investigators active today, we are seeing a profession evolve from a primary concern with two still highly prevalent, painful, and costly dental disorders to one prepared to address all the diseases and disorders that affect all the orofacial tissues.

Mr. Chairman, the FY 1991 request for the National Institute of Dental Research is $140,520,000. I will be happy to answer any questions.

HARALD LÖE, D.D.S.
Director, National Institute of Dental Research

July 19, 1926, Steinkjer, Norway

Education: Oslo University, Norway, D.D.S., 1952: Dr. Odont, 1961

Professional History: 1974-1982, Dean and Professor of Periodontology, School of Dental Medicine, University of Connecticut, Farmington. 1972-1974, Professor of Dentistry and Director of the Dental Research Institute, University of Michigan, Ann Arbor. 1962-1972, Professor of Dentistry and Chairman, Department of Periodontology, Royal Dental College, Aarhus. 1971-1972, Associate Dean and Dean-elect, Royal Dental College, Aarhus. 1966-1967, Visiting Professor of Periodontics, Hebrew University, Jerusalem. 1956-1962, Research Associate, Norwegian Institute for Dental Research, Oslo. 1960-1962, Associate Professor, Department of Periodontology, School of Dentistry, Oslo University, Oslo. 1959-1962, University Research Fellow, Oslo University, Oslo. 1957-1958, Fulbright Research Fellow and Research Associate, Department of Oral Pathology, University of Illinois, Chicago. 1952-1955, Instructor in Operative Dentistry, School of Dentistry, Oslo University, Oslo.

Honorary Doctorate Degrees: University of Toronto, 1989; Royal Dental College, Copenhagen, 1988; University of Medicine & Dentistry of New Jersey, 1987; University of Maryland, 1986; University of Bergen, Norway, 1985; Georgetown University School of Dentistry, Washington, D.C., 1983; University of Lund, Sweden, 1983; Catholic University of Leuven, Belgium, 1980; University of Athens, Greece, 1980; Royal Dental College, Aarhus, Denmark, 1980; University of Gothenburg, Sweden, 1973.

Honors, Awards: Honored by His Majesty the King of Norway (Royal Norwegian Order of Merit), 1989; U.S. Surgeon General's Exemplary Award Medal, 1988; Swedish Dental Society International Prize, 1988; Honorary Professorship, Medical Sciences University of Beijing, 1987; The Royal Dental College, Copenhagen, Denmark, 1987; Goldstein Lecture, Emory University, 1986; Member, National Academy of Sciences, Institute of Medicine, 1985; Benjamin J. Robinson Lecture, University of Maryland, 1985; Alfred C. Fones Medal for Outstanding Achievement in the Service of Humanity, 1984; International Award of the Friends of the University of Connecticut School of Dental Medicine, 1983; Lister Hill Memorial Lecture, University of Alabama, 1983; Daniel F. Lynch Award, Dental Society of Greater Waterbury, 1983; International Lecturer of the Year Award, Academy of International Dental Studies, 1983; Gold Medal, University of Ghent, 1982; Centennial Award, University of California School of Dentistry, 1982; Award of Merit, Hartford Dental Society, 1982; Irving Glickman Memorial Lecture, Tufts University, 1979; William J. Gies Award, American Academy of Periodontology, 1978; Arthur Merritt Memorial Lecture, Baylor University, 1977; Certificate of Achievement, Connecticut Society of Periodontists, 1976; Massachusetts Dental Society International Award, 1973; honored by Her Majesty the Queen of Denmark (Knight of Danebrog), 1972;

International Association for Dental Research Award for Basic Research in Periodontics, 1969; Honorary memberships in several professional societies around the world.

Other Professional Activities: Author of more than 260 scientific articles; international lecturer; honorary member and elected fellow of scientific and learned societies here and abroad.

BROADENING THE NIDR MISSION

Mr. NATCHER. Thank you, Dr. Löe.

Now, Doctor, much of your statement and budget discusses, as you know, problems of oral health rather than dental health.

Is the Institute attempting to develop a broader mission for itself in the future?

Dr. LÖE. Actually, Mr. Chairman, this mission has been developing over the entire history of the Institute. We have not, as a research organization, been confined to only tooth decay and periodontal diseases.

We have had a basic program that relates to most of the tissues of the entire body, including the mouth, and some of the disorders and diseases that may reflect on the mouth in the course of development, maturation, and aging.

We are now codifying something that has been at work over the last 40 years. We feel that, at this point, it's very important, both for the Institute and for the dental profession, to realize that our responsibilities go beyond the confines of tooth decay and periodontal diseases.

LONG-RANGE RESEARCH PLAN

Mr. NATCHER. Doctor, when will the Institute release the long-range research plan for the 1990's, which I believe was to be completed probably this spring? When, Doctor?

Dr. LÖE. Mr. Chairman, that plan has been in development over the last year and a half. We expect it to be in print by May of 1990 so we can use this long-range plan, not only as a blueprint, but also as a guide for the priorities that we have set for the decade.

Mr. NATCHER. An earlier draft of this report establishes the goal, and I quote, Doctor, "to finish the job of eliminating what have been the leading dental diseases—dental caries, periodontal disease, and with them the leading causes of tooth loss."

Dr. Löe, what is your prognosis for meeting this goal?

Dr. LÖE. I am not going to promise you a complete eradication of tooth decay and periodontal disease in our people, but I am going to promise you that, within the next few decades, we are going to see considerable improvement in the oral health of the adults and the elderly.

We have made tremendous headway in improving the oral health of our children. This has been the first order of business for this Institute over the past 40 years, and we have come to a point where half the schoolchildren of America, those between 5 and 17 years of age, have never had any cavities, never had a filling, and the other half have much less disease than their agemates had 10 or 15 years ago.

This is a dramatic improvement in the oral health of young America. What we would like to see now is an emphasis on prevention and early treatment of caries and periodontal diseases in adults and the elderly. We know that these two diseases are the main causes of tooth mortality or tooth loss, so by controlling them, we feel that we will have a major handle on the retention of the natural teeth for a lifetime. That is going to be our goal.

Mr. NATCHER. Will the long-range plan propose any substantial changes in the use of the various research mechanisms available to the Institute such as your centers or training programs, Doctor?

Dr. LÖE. Mr. Chairman, I think at this point we have a fairly good balance to our programs. We submitted to this committee, about 5 years ago, both a long-range plan for our centers development and for research training, including the dentist scientist program that this committee has supported all through the past 5 years.

Our goal would be to broaden our scope and to use all the mechanisms that we have available to achieve these goals, including an emphasis on investigator-initiated research project grants, on research centers where we need to get on with a critical mass of people with certain problems, and on research training programs in order to see to it that the academic institutions get the type of people that they need to sustain the research effort.

In our long-range plan we have also described a series of clinical trials that we need to do in the 1990's in order to move information from basic research into application. We have a problem in the sense that most of our knowledge of clinical problems relates to children; now we have to start testing some of the prevention methods, used in children with such success, on adults and senior citizens.

BUDGET PRIORITIES

Mr. NATCHER. The American Association for Dental Research has submitted a plan for a 50-percent increase in your budget. This proposal is somewhat surprising, however, Dr. Löe, in that it does not propose that any of this increase go toward training, or to inhouse research at the Institute itself. Dr. Löe, are these lower priorities?

Dr. LÖE. No, I don't think that our intramural program is a low priority. We have had a strong intramural presence—a basic research program that has always been very important to the Institute. I also think it has been important to the extramural community. The AADR plan recommends the maintenance and sustenance of that program, as well as our programs in research training and career development.

I think that the AADR speaks to both a strengthening of extramural effort and to maintaining a strong intramural activity. There is not much discrepancy between the AADR priorities and those that are reflected in the President's budget.

THE FLUORIDE CONTROVERSY

Mr. NATCHER. Dr. Löe, as you know, this committee has followed for many years the controversy regarding water fluoridation programs. What can you tell us about the recent findings by the National Toxicology Program that this practice may be associated with increased risk for certain cancers? What about that, Doctor?

Dr. LÖE. Well, I would have to start back 40 or 50 years ago when the fluoride issue emerged as a research topic for this Institute. The first water fluoridation took place in the 1940's, so we have about 50 years of experience with water fluoridation in this country. During the 1950's and 1960's, there was much research going on in terms of the mechanism of action of fluoride, as well as the efficacy and safety of water fluoridation as a very special method of prevention of tooth decay.

Throughout the history of water fluoridation, there have been discussions, and even controversy, as to this approach to prevention of tooth decay. In 1977, NIH agreed to conduct a toxicology study, and the National Toxicology Program has now completed a 2-year study in rats and mice.

There is a long answer to your question, and there is a short one. I want to give you the short one, but I would like to include for the record some of the details that I believe are appropriate in relating the whole story.

[The information follows:]

NATIONAL TOXICOLOGY PROGRAM DATA ON FLUORIDE

The National Toxicology Program (NTP) has released preliminary data from a study on the possibility of a relationship between sodium fluoride and cancer in rodents. The 2-year study exposed rats and mice to very high doses of sodium fluoride. This standard method enables scientists to detect rare events. At the highest levels, which greatly exceed the amount used to fluoridate drinking water, there were some cases of osteosarcoma found in Fisher rats. At this time, the data have yet to be analyzed, interpreted by experts, or subjected to peer review by outside scientists.

During the next several weeks, the NTP staff will release their detailed analysis on the data. Outside scientists will review the data and the NTP analysis and will present their recommendations at a public meeting April 26. Until then, the significance of the test results cannot be determined.

We are also aware of preliminary results from another 2-year rat bioassay by the Proctor and Gamble Company in which Sprague-Dawley rats received high doses of sodium fluoride in their diet. This study found no evidence of any benign or malignant bone tumors. Like the NTP study, however, the study must still undergo scientific peer review and publication.

In short, the entire data must be fully analyzed to determine their significance. Until the completion of this process, the many benefits of fluoride warrant continuation of the present policy designed to prevent tooth decay. It should be pointed out that, after 45 years of water fluoridation involving scores of human epidemiological studies both in the United States and in other countries, there has not been any evidence that shows a relationship between fluoridation and cancer or other diseases in humans.

REVIEW OF TOXICOLOGY DATA

Mr. **NATCHER**. Thank you, Doctor. Now, as you know, a recent article in Science also questions the benefits of water fluoridation. When you get the record back, you will want to put a good answer in there for us, Doctor. You know about this article?

Dr. **LÖE**. Yes, I do, and I was going to say that the data that we have received from the National Toxicology Program is preliminary. They describe pathology observed in rats that have been fed various dosage levels of fluoridated water over 2 years—their life span.

So far, the only significant difference between controls and rats fed low levels of fluoride in the drinking water—as compared with rats fed mid-level and high dosages of fluoride, 45 times and 79 times the recommended levels of fluoride in human drinking water respectively—is that four rats out of 80 in the high level dosage and one out of 50 in the mid-level group came down with a very rare bone cancer. None appeared in the low level and in the control group. It is interesting that the cancers all occurred in the male rats, not in the female rats.

These data are now subject to review and interpretation by scientists and by scientific counselors of the National Toxicology Program to be completed in April of this year. After that time, we will have a much better handle on the significance of the situation.

I should mention to you, Mr. Chairman, that the Secretary of Health and Human Services has established a committee that will review the data from the National Toxicology Program; this review will be completed by the middle of June of this year.

As one who has been living with this issue for almost my entire professional life, I would have to say that these preliminary data go against the massive data that have accumulated over 40 years of research. At this point there is no reason for panic among those who have water fluoridation. We will have to watch the data as they evolve and develop, but as of today, we don't see that there is any reason to terminate any programs on the basis of the data that are available so far.

Mr. NATCHER. Thank you, Doctor.

Mr. Conte, I yield.

RESEARCH AND ACTION PROGRAM

Mr. CONTE. Dr. Löe, I want to welcome you back to our committee and I especially want to congratulate you for the many achievements in the field of dental health.

King Olav of Norway awarded you with the Order of Merit this past year, and I can't think of anyone who deserves that honor more than you do, Doctor.

Dr. LÖE. Thank you very much.

Mr. CONTE. Can you fill us in where your Institute stands in making oral education outreach efforts?

Dr. LÖE. In 1988 we suggested to this committee that a major initiative should be to address some of the problems of older Americans, and this committee appropriated $500,000 to start a program in this area. We have refined the plans and the concept of this research and action program, and during 1990 we will be adding on to this program. We hope that we can continue in 1991, mounting a program that will be of clinical significance to the older segments of the population.

Mr. CONTE. What strategies are you using for pursuing to reach the elderly people?

Dr. LÖE. At the moment we have started within the governmental agencies; we have joined with the Centers for Disease Control and with other Public Health Service agencies that are interested in this problem, including the Indian Health Service and the state and territorial dental directors. In this way we are trying to establish, at least within the government, a coalition that will be able to take some of these issues from the research stage into implementation.

We hope to broaden the scope of this activity to include the American Dental Association, the American Association of Dental Schools, and voluntary organizations among the elderly and among the adult citizens.

This is going to be a real community effort in the final analysis.

CLEFT LIP AND PALATE

Mr. CONTE. I understand that cleft lip and cleft palate are the most prevalent birth defects affecting the face and the mouth. Have you been able to increase research efforts to address the problems, and will you be able to look at other kinds of birth defects at these centers as well?

Dr. LÖE. As I mentioned in my opening statement, Mr. Conte, there are approximately 6,000 births a year in America with cleft lip, cleft palate, or a combination of the two, making this one of the most prevalent birth defects that we have to deal with. We have, over these many years, developed experiences in the treatment and management of these patients, both surgically and post-surgically, including speech and some of the other rehabilitations that need to be taken care of

Last year we established three new craniofacial research centers that are going to capitalize on some of the developments in molecular biology and try to get to the genetic and congenital bases for these birth defects. We know, for instance, that Asians have higher percentages of cleft lip and palate than Caucasians and that blacks have fewer births with these defects than whites. There is an interesting distribution of these deformities, and that is one part of the research agenda.

We will also use genetic research opportunities to get closer to the causes of these developments, and, along with that, we are going to improve the treatment of these patients, because what is going on in research on regeneration and wound healing at the moment would have application to the success of the treatment of these patients.

ECTODERMAL DYSPLASIA

Mr. CONTE. In your opening statement, Doctor, you mentioned children born with an inability to grow teeth. What can be done to help these children?

Dr. LÖE. These children have ectodermal dysplasia, which involves more than just the misshaping of teeth or the absence of tooth germs. Also included are problems with the skin, with the hair, with sweat glands, and a few other things. These children have grave difficulties in controlling their temperature, because they have no sweat glands.

The problem with treating these patients had been that we had to make dentures for them. Because the children were growing, the dentures had to be replaced frequently in order to keep up with their normal growth curves, and of course dentures are really no substitute for real teeth in growing children. During the last 5 years, we have seen the development of implants for these young growing children. When these implants and devices are put into their jaws, the bone grows around the implants and provides stability for construction of either a bridge or some dental device that can provide a much better basis for chewing and other functions of the mouth. This is a tremendous improvement in the treatment of these patients.

PEDIATRIC AIDS

Mr. CONTE. It certainly is. As you know, Dr. Löe, I am concerned about the growth of pediatric AIDS in America, and we have a growing population of these children who are living longer than in the earlier days of the epidemic. What do we know about the oral complications of AIDS in these children, and should the NIDR programs be expanded to include an initiative in pediatric AIDS?

Dr. LÖE. We have of course been part of the AIDS research effort since the very beginning of the epidemic.

Mr. CONTE. I know you have.

Dr. LÖE. And we have, in the course of these past 8 years, accumulated a considerable amount of data on the adults with AIDS, especially homosexuals and intravenous drug abusers. We see a variety of pathologies in the mouth at various stages of development of this disease. Our experience with children is much less.

Over the last 2 or 3 years, however, we have begun to see some of the same problems in children and infants as we see in the adults. There is an overgrowth of yeast and other bacterial infections in these children that is similar to what one finds in the adult patients. There are also developmental problems with these children, in terms of the structure of the teeth and the jaws.

We have just started to be involved in the children's area relative to the AIDS research activity. But we will have to continue.

Mr. CONTE. Well, for the record, because I am running out of time, last year you mentioned that there was a promise for finding a diagnostic marker for the AIDS virus in saliva, and can you bring us up to date on your research efforts in finding and developing that, you can get that for the record.

Thank you, Mr. Chairman.

[The information follows:]

DIAGNOSTIC MARKER FOR HIV IN SALIVA

Reliable diagnostic markers in the oral cavity for determining infection by HIV were reported last year. These included oral candida, hairy leukoplakia, and oral Kaposi's sarcoma. These markers are highly predictive of the AIDS sequelae. Industry is currently developing methods for identifying HIV antibodies in saliva. If successful, this will serve as an alternate method for determining HIV infectivity.

ORAL HEALTH IN MINORITIES

Mr. NATCHER. Mr. Stokes, I yield.

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Löe, I was impressed with the statement made in your formal statement on page 6. You say, "We are especially mindful of the need to improve the oral health of racial and ethnic minorities." Then you go on to tell us that last May you invited a distinguished group of black, Hispanic, and Native American health professionals to discuss health issues and ways to resolve them. Can you give us some idea of what type of suggestions those distinguished black and Hispanic and Native American health professionals gave you?

Dr. LÖE. We had a very effective dialog about the situation among several minorities relative to oral health. I think we all agreed that we do not have a real handle on how much disease exists in the different minority groups, and that the first order of business would be to try to get as much information as possible as to the magnitude of the problem.

As a result of the national surveys that we have conducted over the years, however, we do have some notion of both the prevalence and the severity of oral disease. For example, there is no question in our minds that there are more oral health problems in the minorities than in the white population of this country.

The black children have been doing reasonably well with tooth decay, and we feel that that is because of water fluoridation and some of the other fluoridation programs that we have had all along.

However, the difference between the black and the white child is that, when a black child gets a cavity, there is frequently almost no treatment of it. This later develops into a real problem for the family, as the years go by without treatment. So there is a treatment need that is different as the children develop.

There is also evidence that we have from a recent survey, that would indicate that there is more periodontal disease among black children than among white children, and that some of these children are actually losing their teeth before they get to 18 years of age. This is another target area where we need to explore possibilities of getting epidemiological data, but also to conduct research on the causes of these disease developments in minority groups.

We have decided that we are going to continue the discussion, and that we very soon will have a request for contract proposals concerning the collection of oral health data among minorities. We hope that this contract can be awarded in the course of this fiscal year or, at the latest, 1991.

ATTRACTING MINORITIES INTO DENTAL RESEARCH

Mr. STOKES. Good. Now, are you also doing something in terms of an initiative to attract more minorities into dental research?

Dr. LÖE. Yes. We are part of an NIH effort, both in terms of bringing new groups of people into research, starting at high school or college level, and, in our case, at the professional level of the dental school, in trying to get minorities interested and attracted to scientific careers.

We are also enthusiastic about a minority supplement that we are able to support in our grants activity. We have used that mechanism to augment grants in several areas of the country in the course of the last 2 or 3 years. I think that is an excellent method whereby we can bring a minority scientist into a mainstream scientific activity at an already established research institution, and in this way participate in the development of a scientific career.

USE OF DENTAL X-RAYS

Mr. STOKES. Doctor, today in most dental offices they utilize X-ray machines. Are there any dangers from the utilization of those machines?

Dr. LÖE. As you know, the NIDR has no regulatory authority or function in the area of radiation. In a general sense, I agree with you that there has always been some danger in subjecting people to ionizing radiation, from the beginning of the discovery of the Roentgen rays. In recent history, however, I am not aware of any abuse or any misuse of X-rays, compared to earlier years when dental offices perhaps relied too much on X-rays and took them too often.

I would maintain that the profession is now very responsible relative to the use of X-rays, stressing clinical examination with occasional confirmation by X-rays. We don't see as much X-ray exposure as we did some 20 or 30 years ago.

SALIVA AND HIV

Mr. STOKES. In your opening remarks, you stated there were substances in saliva that would prevent HIV infection. What can you tell us about this research?

Dr. LÖE. About 4 or 5 years ago, it was clear that there was no indication that anyone had contracted AIDS through oral transmission. Even with sharing of toothbrushes and other utensils in the family, nobody seemed to be transmitting the disease through saliva. Also, children with AIDS who have communicated extensively with other children without AIDS didn't seem to transmit the disease.

This was a mystery. Clearly, AIDS was transmitted through bodily fluids, but not saliva. So we embarked on a study of saliva relative to the presence of the virus and the possible reason why transmission didn't occur. At this point we have not identified a substance that may be the cause of this lack of virus in the saliva.

However, there is a recent report on an enzyme called secretory leukocyte protein inhibitor, SLPI, that seems to prevent the virus from getting into the cell.

If you apply saliva to cell culture and then apply the virus, this inhibitor will prevent the virus from entering into the cell. That could be one of the reasons why the virus is not transmitted from mouth to mouth.

We are continuing to work on this and have several responses to a recent Request for Applications on this subject. We will make our selections very shortly so we can get on with this research and try to explain this very important characteristic of saliva.

The significance of this research is quite conspicuous in the sense that, if we could explain why the mouth doesn't permit transmission, we could have a solution to some of the mysteries of HIV infection.

Mr. STOKES. Very interesting. Thank you very much, Doctor. Thank you, Mr. Chairman.

Mr. NATCHER. Mr. Pursell, I yield.

TOXICOLOGY STUDIES ON FLUORIDE

Mr. PURSELL. I am going to be very brief.

You answered some of the questions, Dr. Löe, to the Chairman on the toxicology study.

My dental community has a high regard for your Institute and our clinics around the country and our centers. I am very impressed with the dental community keeping up to date with the state of the art in dentistry.

They read the journals and attend their classes. I am quite encouraged with their current state-of-the-art in the field of dentistry.

I think from bottom to top, top to bottom, I think there is a lot of good communication there in educational research and basic research that gets out into the field. I like that. I think it is a pretty good dimension.

On the study itself, did you indicate when the study would be completed? Is the study near completion?

Dr. LÖE. The National Toxicology Program study?

Mr. PURSELL. Yes.

Dr. LÖE. That study is completed. The analysis of the data is not completed as yet. This will occur in the month of April so that by May we may have the data.

Mr. PURSELL. You may have the data. You don't know for sure?

Dr. LÖE. I think that is——

Mr. PURSELL. Pretty fair assessment?

Dr. LÖE. Yes.

Mr. PURSELL. Then you will appoint a panel to review that data?

Dr. LÖE. The Secretary of Health and Human Services and the Assistant Secretary for Health have already established a committee. The former Commissioner of the Food and Drug Administration, Dr. Frank Young, is chairman of that committee.

He is going to get all the data from the National Toxicology Program, from the National Cancer Institute relative to the human situation around the country, and also obtain data from the international scene.

Mr. PURSELL. How long will that take?

Dr. LÖE. They have promised they would have the report during the course of the summer.

Mr. PURSELL. Of this summer?

Dr. LÖE. This summer, that is right. In June.

Mr. PURSELL. When would final recommendations become public?

Dr. LÖE. We expect that shortly thereafter the Secretary would have had time to review the material and make some recommendations.

Mr. PURSELL. Late summer, fall?

Dr. LÖE. I think early fall.

Mr. PURSELL. Maybe during the lame duck session?

Dr. LÖE. It isn't designed that way, but that may happen. I really don't know exactly when the Secretary is going to announce the recommendation, but we expect it to be summer or early fall.

Mr. PURSELL. Thank you.

That is all I have.

Mr. NATCHER. Mr. Early, I yield.

NIDR INVOLVEMENT IN ECONOMIC SAVINGS

Mr. EARLY. Thank you, Mr. Chairman.

I, too, want to welcome you, Doctor.

Dr. Löe, in your statement you have suggested that the American people have saved billions of dollars with regard to the delivery of dental care, and I agree with that. I think that is assumed or taken for granted.

I don't think there is one particular reason why it happened or one individual who thought it out.

Do you give the National Institute of Dental Research any credit for that?

Dr. **Löe**. I would have to do that.

Mr. **Early**. Right on that.

Dr. **Löe**. The establishment of this Institute in 1948 by the U.S. Congress was a monumental action that set in motion a tremendous research activity and a prevention activity that is very important.

Mr. **Early**. Do you think fluoride would have progressed as fast as it did without your confirmation and assurance to the American people?

Dr. **Löe**. No. The other part of the story is that there also has been a profession out there that has been able to use the information and apply it in practice. The dental profession is prevention oriented.

The public is also interested in maintaining oral health. We see it in the recent statistics that 80 percent of employed Americans see the dentist on a regular basis. That is a tremendous interest.

Mr. **Early**. What happened to diminish caries in just everyone? Isn't that really something that you people laid on as far as American people?

This is why they have saved so much money. As the world changes, we have more contact with African nations, and poor countries like Nicaragua, the Baltic States, where people have not had anything like this available to them.

I am sure that they have the same kind of problems the United States had years ago, and I would think your Institute should be able to submit data to them that would be beneficial to them and save so much.

Dr. **Löe**. I think your notion is a good one. We have been working with the World Health Organization for many years and have participated in the dissemination of knowledge and information to the developing countries. We also directly participate in some of the planning of the programs for——

Mr. **Early**. I think that when you do that for countries over a number of period of years, those poor people are going to realize that the United States really contributed to improving their health conditions.

Dr. **Löe**. We have a backlog of needs in the Eastern European countries that we already have started to do something about. We will have the first meeting between this Institute and the Institute in Moscow in 1991. It will deal with some of the issues they really need to know more about in order to do a better job with their oral health problems. We are looking forward to that interaction.

CLINICAL TRIALS

Mr. **Early**. Are there any new clinical trials in the 1991 request?

Dr. **Löe**. No, sir.

Mr. **Early**. Are there any ready to go but not funded in the 1991 request?

Dr. **Löe**. Yes, sir. We have some 30 or 40 clinical trials on the back burner, so to speak, that we hope to conduct over the course of the 1990's.

MATERIALS SCIENCE RESEARCH CENTERS

Mr. EARLY. Regarding the new materials science research centers, what can you tell us about the advances in new materials products?

Dr. LÖE. We have seen quite extensive advances in the materials sciences over the past years. Quite naturally, the whole technology has been moving rapidly.

As far as we are concerned, we would very much like to see dental materials that would substitute for the silver and the gold that we used in the past and to use more synthetic materials that will be more esthetically acceptable, but also would have the durability that we have seen in gold and silver.

The goal of the new centers is to develop new materials that would be both acceptable from a safety point of view but also have the efficacy that would be compatible with the criteria we set.

Mr. EARLY. Is there any coordination or collaboration with the National Institute of Standards and Technology?

Dr. LÖE. We have supported a program in dental materials at the National Institute of Standards and Technology for many, many years.

Last year we awarded a grant for a materials science center in the Institute.

MUSCLE REGENERATION

Mr. EARLY. Bring us up to date with regard to your advances in the understanding of optimal conditions for the transmission and regeneration of the skeletal muscles and treatment of facial injuries and paralysis?

Dr. LÖE. I would like to give you that information for the record.

Let me say that those advances are part of the research and development we have on regeneration of muscles and connective tissues. Capacity for regeneration of muscles is going to be very important in dealing with some of the wounds that we treat in the face and in the head and neck.

Mr. EARLY. Will you expand for the record?

Dr. LÖE. I shall be pleased to do so.

[The information follows:]

MUSCLE REPAIR AND TRANSPLANTATION

The Institute has supported research at the University of Michigan School of Medicine dealing with two of the biggest clinical challenges in muscle repair and transplantation. One is to ascertain the optimum conditions under which a muscle can be repaired and regain its strength. Both clinical and basic research have demonstrated that larger muscles can be transplanted with greater recovery of normal function if the nerves and blood vessels are repaired immediately with microsurgical techniques. Further research in this area is essential since there is still controversy over which procedures are most beneficial.

The second challenge is to learn why the 95 percent of muscles that do survive a transplant do not regain their full capacity. Our researchers think that the clue lies in correctly repairing the nerves. By using animal models to study different ways to repair muscle nerves, they hope to discover which techniques hasten or inhibit the return of muscle performance.

This research will aid in answering the questions regarding repair and transplant of facial muscles. Injuries in the craniofacial region occur as a result of head injuries sustained in automobile accidents, Bell's palsy, reconstructive operations to the head and neck from cancer, as well as other causes. The transplantation of limb muscles into the face are among the most challenging problems for reconstructive surgeons.

Mr. EARLY. I would like to see more detail on that.

Are there implications for other areas of research?

Dr. LÖE. Yes; this research goes far beyond the face and has orthopedic implications.

DOWNWARD NEGOTIATIONS

Mr. EARLY. Doctor, I really belabored the downward negotiations with the other directors. Yours certainly is substantial. It isn't that I think your Institute is any less important. I think you have made so much progress.

As I asked the other directors, I knew what downward negotiations were anticipated, but I was trying to make a point. I have several questions on that which I would like to be answered for the record.

Dr. Löe, you really have produced a fine—dental research has opened up a lot of opportunities. I think there are many other opportunities, more than just health application.

I mean abroad for us. I really hope we spend a few dollars and take advantage of that. I think your Institute does an outstanding job.

Dr. LÖE. Thank you.

Mr. EARLY. Thank you, Mr. Chairman.

Dr. Löe, we want to thank you and your associates for appearing before our committee at this time on behalf of your budget request for the fiscal year 1991. It has been a good hearing, Doctor.

Dr. Raub, all of our hearings have been good. We appreciate it. We want you to know it.

Dr. RAUB. Thank you, sir.

[The following questions were submitted to be answered for the record and the justifications follow:]

RESEARCH CENTERS

Mr. Natcher. Five years ago you submitted a report to this Committee on use of centers. Since that time the number of center grants has increased from 13 to 21. Do you still believe that putting this money into centers rather than grants is the best strategy?

Dr. Löe. Although the number of centers has indeed increased, the funding for this mechanism as a percent of our budget has actually decreased. When the report was submitted to the Committee in 1985, the centers line represented 13 percent of the total budget; in the 1991 request, funding for centers is only 11 percent of the total. Funding for research project grants has remained at 46 percent over that same period.

We believe that the centers mechanism has been very valuable in facilitating oral health research and affording opportunities for research training, and would like to see the number of research centers increase to 30 in the 1990's, as recommended in the 1985 report to this Committee.

Mr. Natcher. Would you describe for us briefly the two new center grants which are to be awarded in 1990?

Dr. Löe. The Core Center Program is a mechanism to develop state-of-the-art clinical research centers in our Nation's dental schools and dental research institutions by supporting shared resources and facilities (core units) for a number of investigators. The intent of the program is to encourage increased collaboration among basic and clinical scientists and to expedite the translation of knowledge and advances in biomedical and behavioral science into new and better methods for improving the oral health of the Nation.

Mr. Natcher. Are all center grants awarded through a system of open competition?

Dr. Löe. All NIDR competitions for new center grants are advertised for open competition through a Request for Application (RFA) announcement in the NIH Guide for Grants and Contracts. Five-year competing renewals of ongoing centers are similarly advertised for open competition through an RFA issued prior to renewal. In this way new applicants are invited to compete with previously funded center grantees. Both new and competing renewal applications for centers are reviewed for scientific merit in the same uniform manner. After review, applications from ongoing center grantees and those from new applicants compete for funding on the basis of their scientific merit and programmatic relevance and on the availability of funds.

MERCURY AMALGAMS

Mr. Natcher. Doctor, is there a problem with mercury used in dental fillings?

Dr. Löe. We have critically reviewed the literature on the potential hazards of using mercury in dentistry. We conclude that, while there is consistent evidence indicating release of mercury vapor from restorations during chewing, tooth brushing, and other activities, proof of a causal link of this source of mercury to any human health problem is lacking.

The most common sources of mercury are foods, contaminated air, occupational exposure, and certain drugs and ointments. It is very difficult to differentiate the effect of one of these sources from that arising from dental amalgam. Examination of blood and urine levels of mercury of individuals with and without amalgam fillings has shown the contribution from amalgam fillings to be negligible. A recent NIDR-supported study confirms earlier findings; neither mercury itself nor a metabolite, methyl mercury, could be detected in the blood or urine of any of 31 patients over a 1-year period after placement of up to eight mercury-containing amalgam restorations.

There is no documented evidence for recommending that the use of mercury-containing dental amalgams in restorative dentistry be discontinued. The removal of dental amalgam can only be recommended in those patients who have true hypersensitivity to mercury or other constituents. The Institute continues to solicit applications for research on this topic.

DENTAL IMPLANTS

Mr. Natcher. Doctor Löe, what can you tell us about recent concerns about the use of dental implants. Is there a problem with severe infections?

Dr. Löe. Recent concerns about the use of dental implants have focused on: 1) the marketing of dental implant systems without sufficient clinical trials to demonstrate efficacy, and 2) the nature of the training necessary for a clinician to place dental implants.

There does not appear to be a problem with severe infections related to dental implants when they are placed by well-trained clinicians (e.g., those trained in the surgical specialties such as oral and maxillofacial surgery and periodontics). The incidence of infection probably varies somewhat with the design and material of the implant. For instance, infection associated with the commercially pure titanium endosseous screw implant is extremely rare. There have been more reports of infection with subperiosteal and plate (blade) implants.

SALIVA TESTING

Mr. Natcher. Have you investigated whether tests of saliva could be used to determine drug or alcohol use instead of using blood or urine testing?

Dr. Löe. Saliva has long been recognized by forensic scientists and clinical investigators as a potentially important medium for monitoring levels of naturally occurring body chemicals, such as hormones, as well as medications (e.g., antiepileptic and heart drugs) as well as drugs of abuse. The use of an easily accessible fluid for drug testing would avoid invasive or embarrassing procedures and might be less expensive. While there have been promising clinical studies to test the use of saliva in drug assays, more remains to be done. In part, this situation reflects the growth of research in this area and the discovery of new salivary components. The role of these components, how they vary genetically from individual to individual, and how they, as well as the fluid part of saliva, interact with drugs, require further elucidation.

DENTIST-SCIENTIST PROGRAM

Mr. Natcher. I understand that the first class from the dental scientist program will graduate this spring. Can you tell us how many of these individuals will go into research on a full time basis?

Dr. Löe. The application process for individuals to enter the dentist-scientist program has been extremely competitive. It has been, in a sense, a self-selection process; i.e., only the best and the brightest have applied, and from those, only a few individuals can be selected. Part of the selection process includes an evaluation of the individual's commitment to a career in the academic arena that involves a research/teaching/clinical activity. Therefore, it is not surprising that all grantees intend to follow this course of action upon graduating from the program.

Mr. Natcher. Have you designed an evaluation system to determine the effectiveness of this training program in terms of their future success in getting R01 grants?

Dr. Löe. Yes; we have developed an evaluation system to determine the success of the program. We plan to compare the accomplishments of the dentist scientists from the institutional and individual programs to several control groups over a period of 10 years.

Currently, baseline data about such measures as success in obtaining R01 grants from NIH, publications and citations to them, other awards and honors, academic appointments, etc., are being compiled on four control cohorts of trainees supported by the NIDR since 1980: recipients of the individual NRSA; individuals supported through the institutional NRSA; recipients of the physician scientist award for dentists; and full-time researchers in dental schools who have never received training support from NIDR. Data from these groups will comprise normative values for use in measuring the actual accomplishments of the dentist scientist awardees.

In addition, we will form matched comparison groups, where possible--consisting of a dentist scientist, NRSA recipient, physician scientist, and non-NIDR-supported researcher--based on age, level of training, sex, and research area. These groups will be followed for a 10-year period and evaluated in terms of research accomplishments.

Mr. Natcher. What is the current annual cost of the dentist scientist program?

Dr. Lőe. The current annual cost of this program is approximately $6.2 million.

Mr. Natcher. Where in the budget is the cost of this program shown?

Dr. Lőe. The dentist scientist program is included in the "Research Career" line under "Other Research Grants."

JUDGING QUALITY OF GRANTS

Mr. Natcher. Dr. Raub, this is a problem for all of the Institutes. In the past we have used paylines and approval rates to judge relative quality. Now you have switched to a percentile system which is hard to explain and even harder to understand. Can any of these systems be used to compare relative quality over time or among the Institutes?

Dr. Raub. We regret that the percentile system is causing confusion. We changed to this system to deal with the diversity of rating behavior among study sections and because of priority score "creep," an increasing proportion of scores of 150 or better. The percentile rank now serves as the primary index of relative scientific merit when applications are being considered for funding, although other critically important factors--such as relevance, program goals, portfolio balance, and available resources--are included in the funding decisions of an Institute, Center, or Division. As with any new system, we must build a historical database for percentile paylines to be able to make comparisons over time.

TMJ-RELATED DISORDERS

Mr. Natcher. Last year the Committee heard testimony from several individuals concerned about jaw problems referred to as TMJ. The Committee asked that you increase attention to this problem and consider a possible center grant in this area "if scientifically justified." What actions have been taken to address this concern?

Dr. Lőe. We recently sponsored a conference on differential diagnosis of chronic orofacial pain conditions, emphasizing temporomandibular disorders (TMD). Several expert panels identified major clinical and basic research needs for TMD, and for other persistent oral and facial pain problems. Many of these chronic pain conditions are more common and/or more severe in older people.

The Institute recognizes that the causes and management of chronic orofacial pain conditions, including TMD, need much more study and that dental and medical practitioners urgently need better scientific information regarding these conditions. Consequently, we will publish a program announcement for grant applications and a request for center applications in this area in the next several weeks. This initiative is planned to stimulate basic and clinical research on the pathogenesis, diagnosis, and prevention of chronic orofacial pain conditions, with particular emphasis on TMD.

IMPROVEMENTS IN DENTAL HEALTH

Mr. Natcher. Doctor, for the record we would like you to prepare a short statement describing the overall improvement in the dental health of this country's children and adults. Along with this we want you to put in two or three examples of the important role of your Institute in these accomplishments. That will help us when we go to the floor.

Dr. Löe. The evidence for an overall improvement in the dental health of Americans comes from two nationwide epidemiologic surveys conducted by the NIDR: A survey of working adults and senior citizens in 1985-86, and a survey of schoolchildren between the ages of 5 and 17 in 1986-87. The most impressive finding in the adult survey was that only 4 percent of working adults (between 18 and 65 years old) had lost all their teeth. Half of those employed had lost at most one tooth. With regard to decay, the employed adults averaged 23 decayed or filled surfaces, with approximately 95 percent filled. Decay on tooth roots averaged less than one single decayed or filled root surface per person. The periodontal health of working adults was also impressive. Signs of gum infection were prevalent, but generally these were the mildest forms of disease affecting very few sites in the mouth.

The children's survey revealed that half the 40,000 children examined had no evidence of decay in their permanent teeth--no cavities; no fillings. Furthermore, the children who still have caries have fewer and smaller cavities than did their agemates less than a decade ago. We have estimated that the overall savings in the nation's dental bill brought about by these improvements in the oral health of children and adults amount to $4 billion a year.

We attribute these gains in health to the major discoveries that emerged from dental research over the past four decades. During the first decade of its existence, NIDR supported the clinical trials and experimental studies that established the role of fluorides and water fluoridation in preventing tooth decay. With the aid of the dental professional community, the Public Health Service, and civic leaders, community water fluoridation was adopted in cities and towns across the country, soon followed by the commercial production of fluoride toothpastes, mouth rinses, and other fluoride vehicles. Meanwhile, dental research investigators demonstrated that dental caries was an infectious disease associated with bacteria in dental plaque. They further showed that the bacteria in question converted sugars and starches in the diet to acids that could dissolve tooth enamel. In time, the periodontal diseases also were shown to be infections associated with bacteria in dental plaque.

The dual discoveries that the most common and costly dental diseases were caused by bacteria in dental plaque established the basis for prevention, which has been the critical factor in the improvements in dental health now being enjoyed by the American people. We would add, as well, the overall gains in the standard of living and education that have led to today's better-informed citizens, knowledgeable about the role of diet in disease, committed to oral hygiene, and increasingly going to their dentists for regular check-ups.

There remain pockets of dental diseases in risk groups and problems among our oldest citizens who grew up without benefit of fluorides and perhaps without benefit of a toothbrush. These facts are guiding NIDR initiatives for improving the oral health of adults and older Americans, and for coming to the aid of the children who are especially susceptible to decay. These initiatives will entail epidemiologic studies and research to develop better means of diagnosis, prevention, and treatment that can be applied to all patients. However, the evidence that we have seen a turn-around in the statistics for the diseases that were once considered irrevocable and inevitable has also led to a new look in dental research--a broadening of the scope and depth of our investigations to include all the diseases and disorders that affect the oral tissues directly or indirectly as a complication of diseases or disease treatments affecting other body tissues.

AIDS

Mr. Conte. Last year you mentioned that there is promise for finding a diagnostic marker for the AIDS virus in saliva. Can you bring us up-to-date on your research efforts in finding and developing such a marker?

Dr. Löe. Reliable diagnostic markers in the oral cavity for determining infection by HIV were reported last year. These included oral candida, hairy leukoplakia, and oral Kaposi's sarcoma. These markers are highly predictive of the AIDS sequelae. Industry is currently developing methods for identifying HIV antibodies in saliva. If successful, this will serve as an alternate method for determining HIV infectivity.

ARTIFICIAL SALIVA

Mr. Conte. What are the prospects for developing an artificial saliva for patients who suffer from dry mouth or other diseases?

Dr. Löe. Because of substantial NIDR support over the last several years, investigators have made considerable progress in isolating and characterizing specific salivary proteins and defining their normal functions. Thus, these scientists now understand much about the lubricatory, antibacterial, and tooth-hardening properties of specific salivary proteins. In fact, we even understand which small portions of these proteins carry out the biological functions. For example, human saliva contains proteins that kill the fungus Candida albicans; now we know which small segments of these naturally occurring factors can kill this fungus. It appears that we will be able to make artificial salivas that contain such active natural molecules and will therefore have excellent salivary substitutes.

RESTORATIVE MATERIALS

Mr. Conte. Are we close to finding something better than silver fillings for back teeth?

Dr. Löe. We are currently supporting research to develop new materials and to improve existing, nonmercury-containing dental filling materials. Chief among these are composites or tooth-colored polymers reinforced by ceramic particles. Although composite resins have been improved substantially, they cannot yet be considered as an overall substitute for amalgam as a restorative material. Controlled clinical studies using defined criteria to analyze mechanisms covering marginal breakdown and/or leakage are needed and will be emphasized in FY 1991.

CHRONIC FACIAL PAIN

Mr. Conte. I hear that chronic pain conditions affecting the face and jaw are fairly common. Are there any new developments that can help these people?

Dr. Löe. Scientists have found that recurrent or constant pain in the face and jaws results from several distinct pathophysiological processes involving the temporomandibular joint, the jaw musculature, and processes occurring within the central nervous system. For patients whose pain is primarily attributable to changes in the functioning of the jaw musculature, various medication regimens (e.g., use of nonsteroidal anti-inflammatory agents and of low dosage levels of tricyclic antidepressants) can produce significant pain relief. Physical therapy approaches combining application of heat or cold with muscle stretching can also provide relief and help prevent the development of contractures or muscle-splinting in the masticatory muscles. In general, these muscle pain conditions have been shown to be episodic and not progressive. Thus it is important that clinicians avoid subjecting patients whose pain originates in the jaw musculature to costly and irreversible interventions such as surgery, complete mouth restorations, or permanent occlusal adjustments.

During FY 1990 we will issue a program announcement for grant applications to study the pathogenesis of the different conditions producing chronic pain in the jaw and face, as well as a Request for Applications for Chronic Orofacial Pain Research Centers. The research centers will be expected to clarify the pathogenesis, diagnosis, and prevention of neuralgic and musculoskeletal pain problems occurring in the orofacial region, most of which primarily afflict adults and seniors.

A number of dental schools are revising their curricula related to the management of chronic jaw pain. NIDR scientists will participate in a May 1990 workshop to develop specific curricular recommendations reflecting current scientific knowledge of these conditions. Chronic pain clinics have recently been developed in more than 15 dental schools. An expansion of such programs at other dental schools is under way and should help foster wider understanding and improved management of these conditions.

DENTAL SEALANTS

Mr. Conte. Dental sealants are making an important contribution in preventative dental care. What has your Institute been doing in the field of dental sealants?

Dr. Löe. A quarter-century of NIDR-supported research on dental sealants has found them to be completely safe, highly effective, and very economical in preventing tooth decay. At this stage, our ongoing research is limited to refinements and clinical testing only.

Our concern now rests with communicating the need for sealants to the public. In this vein, we have developed a variety of educational materials (leaflets, posters, bookmarks) about dental sealants for use in educating the public about this preventive procedure. Many of these materials are available in both English and Spanish. The materials are designed for use in private practice and in public settings such as clinics, schools, and health fairs.

In addition, the Institute collaborates with other agencies in developing materials. For example, we have been working with the Ohio Department of Health in the production of educational videos on sealants and with the Massachusetts Department of Public Health in developing a new publication, "Preventing Pit and Fissure Caries: A Guide to Sealant Use."

Mr. Conte. What could be done to increase the use of dental sealants among children?

Dr. Löe. The Surgeon General's office, the American Dental Association, and others concerned with dental health have encouraged sealant use, primarily in communication with dentists and other professionals. Clearly, efforts need to be increased in reaching out to the public, so that parents will begin to appreciate the validity and need for sealant use for their children.

INFECTIOUS DISEASES

Mr. Conte. Can you review what efforts are being made in reducing the incidence of oral herpes?

Dr. Löe. The NIDR annually supports an International Herpesvirus Workshop, which this year will be held at Georgetown University August 2-8. The focus will be on gene regulation, DNA replication and genome structure, AIDS and herpesviruses, virus-cell interactions, immunology, and interventions. Several of our grantees will participate in this workshop. The proceedings, which will provide state-of-the-art technology in drug and vaccine development and directions for future research, will receive wide dissemination within the international research community. It is anticipated that the proceedings ultimately will have a significant impact on reducing the incidence of oral herpes.

Within our intramural research program, the Laboratory of Oral Medicine has pursued a three-fold approach in the treatment and prevention of herpes simplex virus (HSV) infection:

- Development of an effective vaccine against HSV to protect people from becoming infected with the virus. We have collaborated with National Institute of Allergy and Infectious Diseases (NIAID) in the development of a recombinant vaccinia vector that expresses HSV antigens. This recombinant is designed for use as a vaccine against HSV. In animal models this vaccine provides excellent protection against viral infection. However, testing of this vaccine in human clinical trials awaits resolution of various safety issues concerning the reintroduction of vaccinia virus into the human population. We are also exploring the possibilities of using other recombinant live vectors as alternatives to the vaccinia system.

- Testing antiviral agents in the treatment and prevention of active HSV infection. We are conducting a clinical trial, in collaboration with NIAID, in which acyclovir, an anti-herpes drug known to be effective in the treatment of genital herpes, is being tested for its ability to prevent orolabial herpes (cold sores). Patients with a history of frequently recurrent orolabial herpes (six or more episodes per year) are being given either oral acyclovir or placebo on a daily basis to see if this drug can prevent recurrences of herpes labialis. As this trial is a placebo-controlled double-blind study and is still under way, results are not yet available. If this drug proves successful, we could then recommend its use to those selected patients who have very frequent cold sores.

o Identification of factors that trigger and agents that inhibit reactivation of the virus. If one could identify those factors responsible for triggering reactivations of the virus, it might be possible to devise new means of intervening to prevent recurrences. In addition, one could counsel patients to avoid triggering factors or use antiviral agents or other drugs to prevent recurrences following exposure to triggering factors. We have previously demonstrated that ultraviolet light, a component of sunlight, is a potent stimulus in triggering recurrent cutaneous HSV infections. We have recently completed a study in which we demonstrated that acyclovir was capable of preventing UVB light-induced recurrent infection. This model system can be used to test the efficacy of other drugs in preventing recurrent HSV infection.

Mr. Conte. Are there any new drugs being developed that could stop the herpesvirus?

Dr. Löe. Currently supported extramural studies are designed to investigate the role of several classes of chemical compounds that inhibit selected enzyme systems necessary for HSV replication. We are also supporting a promising herpesvirus vaccine development study, which is part of a large program project. The primary effort is directed toward identifying the role of HSV glycoprotein D (gD), a key component of the virion envelope of HSV, in causing viral infection. Recently three U.S. and one foreign patent have been received for the technology related to the use of gD as a subunit vaccine. Two firms have already tested the vaccine in animals for safety and efficacy. The next step is to conduct similar tests in humans.

In the intramural program, a variety of approaches are being taken to prevent initial infection, treat active infection, and prevent recurrences. However, no drug has yet been developed that will eliminate the "latent" (or silent) viral infection of nerve tissue that serves as the reservoir for subsequent recurrent genital and oral infections. Drugs that have shown promise in animal models have to date been too toxic for human use. Recent evidence has suggested, however, that patients with genital herpes who take acyclovir daily for several years to prevent recurrences have a decreased number of recurrences when the drug is stopped. Whether this effect is due to the drug is still not certain. We will be following our patient population taking acyclovir daily to prevent cold sores to see if the same effect occurs in this group. In addition, we are initiating studies on a new drug, capsaicin, which has been reported to decrease the amount of latent virus in nervous tissue of infected animals. Results from these studies will be available within the next 2 years.

SMOKELESS TOBACCO

Mr. Conte. What is the latest knowledge on the oral complications of using smokeless tobacco?

Dr. Löe. In 1986, the NIDR co-sponsored a consensus development conference on "Health Implications of Smokeless Tobacco Use." Currently, investigators at the University of California, San Francisco School of Dentistry, are conducting a landmark study on the oral complications of smokeless tobacco use in over 1,000 baseball players, coaches, and managers. Both the conference and the study indicate that smokeless tobacco use is definitely a risk factor in the development of precancerous and cancerous lesions of the oral cavity. In fact, a recent study of the effects of smokeless tobacco use showed that the likelihood of developing oropharyngeal cancer was 4.2 times higher in users than in non-users. The effects may be mediated by carcinogenic chemicals from smokeless tobacco products acting alone on target tissues or by their synergistic effects with HSV-1, human papillomavirus (HPV), transforming growth factor-alpha, or previously studied oncogenes (cancer genes). Other oral complications of smokeless tobacco use are increased mucosal permeability, decreased salivary flow, and an increased incidence of gingivitis, particularly in adolescents and young adults.

Mr. Conte. Is the Institute involved in public education efforts to reduce use of smokeless tobacco, particularly among young men?

Dr. Löe. Yes; we co-sponsored the 1986 consensus development conference on smokeless tobacco with the NCI that documented the extent of the problem and some aspects related to its amelioration. NIDR staff also participated in the development of the Surgeon General's report on the health consequences of smokeless tobacco in that same year.

In addition, the NIDR has conducted and is supporting surveys that document the extent of the oral manifestations of smokeless tobacco use as well as use patterns. In the 1986-87 National Oral Health Survey of U.S. Schoolchildren, we found that adolescent white males had very high prevalence of smokeless tobacco-associated lesions. A small study in Navajo adolescents showed that over 50 percent of the children used smokeless tobacco products.

Currently NIDR is supporting the oral health component of the NHANES-III (1988-94), part of which is assessing tobacco use and health effects in U.S. citizens of all ages.

TASTE AND SMELL

Mr. Conte. What are some of the efforts being made in looking at the diseases which may affect taste and/or smell?

Dr. Löe. Our intramural researchers have found that a number of disorders or treatments (e.g., Sjögren's syndrome and radiation treatment) involving the oral cavity may affect taste and smell. The extent and causes of taste and smell alterations in these conditions are being determined. Recent studies reveal that taste complaints and measurable declines in taste performance occur frequently in Sjögren's syndrome; these changes are not accompanied by similar declines in smell acuity. Radiation therapy causes rapid and pronounced declines in taste performance, which usually recover within 3 months after treatment ceases.

In the extramural program, NIDR-supported investigators recently found that toothless individuals aged 65 and over were much more likely to report taste and smell disorders than were seniors who had their full dentition. Elderly individuals with diabetes also experienced more taste problems. A newly initiated longitudinal study at the NIDR-supported Research Center on Oral Health in Aging has begun evaluating how the aging process, as well as specific diseases and medications, influence sensory functions including taste and smell, with the overall aim of developing methods to decrease such impairments.

NIDR also continues to collaborate with the National Institute on Aging in the Baltimore Longitudional Study of Aging. NIDR staff are conducting cross-sectional and longitudinal studies of selected individuals who receive oral examinations as well as tests of sensory motor function.

In September 1989, the NIDR issued a program announcement to encourage research on the impact of oral conditions or diseases on taste and smell. We have begun to receive grant applications responding to this initiative.

DENTAL IMPLANTS

Mr. Conte. Dr. Löe, your Institute has looked at dental implants for quite some time now. What have been some of the recent advances in dental implants?

Dr. Löe. The most significant advance during the past two decades has been the development of the two-stage cylindrical, titanium implant inserted via a controlled temperature technique. This basic device becomes firmly attached to the bone and is clinically efficacious. We are now supporting a new program project in which blade-shaped titanium implants placed in the same manner as the successful cylindrical cones are being tested. Blade-shaped implants can be used in areas where the bone is not thick enough for cylindrical implants.

Now that implant therapy is accepted for healthy individuals, there is a need to study the efficacy of these devices in patients with pre-existing medical conditions. Accordingly, the NIDR is conducting an intramural clinical trial on the efficacy of implant therapy in ectodermal dysplasia patients who have congenitally missing teeth. The Institute has also recently funded an application on the efficacy of dental implants in elderly American veterans who have diabetes. Diabetic patients tend to lose teeth early as a result of periodontal disease.

Dental implants placed in the front part of the lower jaw bone have a high rate of success, while implants placed in other parts of the lower or upper jaws are somewhat less predictable.

Accordingly, the NIDR has recently funded a grant to conduct basic studies in animals on implants placed in the different types of craniofacial bone.

Mr. Conte. What is the evidence that shows that implants are effective in the long-term?

Dr. Löe. At a recently held NIH consensus development conference on dental implants (June 1988), the conference panel issued a statement indicating that dental implants can be effective in selected patients for 10 years or more when placed by well-trained dentists. The Panel based its conclusions on a large number of case series studies published during the past two decades.

Mr. Conte. What are the future directions for research on materials and designs of dental implants and on clinical management?

Dr. Löe. The basic designs of dental implants probably will not change since such a large variety have already been considered. However, they will be refined and optimized for different levels of missing teeth and for different regions of the mouth by sophisticated engineering analysis in conjunction with modern materials research. More than likely, cylindrical and blade forms will continue to predominate.

Even though there has been great success in developing materials with a high degree of biocompatibility, there will probably be continued advances made through collaborative efforts between cell biologists and material scientists, particularly those skilled in surface chemistry. At present there is divided opinion among scientists on the superiority of the titanium oxide surface versus hydroxyapatite, the two leading implant surfaces in contact with the bone, soft connective tissue, and epithelium. The question is under investigation currently and should be resolved soon. Moreover, it seems likely that other novel surfaces will be developed that will accelerate attachment to the implant of all the tissues involved.

The exact texture of the implant surface both at the bony interface and the soft tissue interface is another unresolved question that is related both to design and surface chemistry. Determining the desirability of incorporating different surface textures for contact with different tissues has been somewhat slowed by technical difficulties in applying coatings to the basic implant design. However, it is expected that this issue will be resolved within a few years, so that implant surfaces presented to the tissues will be optimized both in regard to chemistry and texture.

Clinical management at present requires special instruments and materials and complicated surgical and prosthetic procedures that extend over periods of months. It is anticipated that the development of improved implants and procedures will enable dentists to provide better service for longer periods at lower cost to a wider variety of patients than is now possible. As a result, dental implants of the future will become suitable for patients requiring local bone grafting, as well as for those with systemic conditions, such as diabetes or osteoporosis.

DENTAL DISEASE AND DIABETES

Mr. Conte. What problems do diabetics have in oral health?

Dr. Löe. Patients with juvenile and adult onset diabetes have major oral health problems. The oral disease most frequently associated with diabetes is periodontal or gum disease. When the periodontal disease is uncontrolled, the teeth become loose and are eventually lost. The worst periodontal disease is seen in patients with poorly controlled diabetes. Other oral health problems seen in these patients include delayed healing of extraction and surgical sites, increased susceptibility to oral infections (such as abscessed teeth), and dry mouth secondary to excessive fluid loss. A dental infection in a poorly controlled diabetic can become life-threatening and result in hospitalization of the patient.

Mr. Conte. What efforts are you making to educate diabetics on the importance of good oral hygiene?

Dr. Löe. The NIDR targets its diabetes education efforts to both the patient and the professional. We developed "Periodontal Disease and Diabetes: A Guide for Patients," a publication that describes in lay terms how gum disease develops, details special treatment considerations, and provides practical information for preventing the periodontal complications of diabetes. An accompanying card, "Dental Tips for Diabetics," summarizes key information in a concise hand-out. These publications have recently been translated into Spanish and are scheduled for printing this spring.

Because periodontal disease is one of the more recently recognized complications of diabetes, the NIDR also produced "Detection and Prevention of Periodontal Disease in Diabetes," a guide for primary care physicians, dentists, and allied health professionals. A coordinating exhibit designed by the NIDR has been displayed at professional meetings, and a clinical slide presentation for health care providers has recently been completed on the oral health complications of diabetes. The printed materials are distributed nationwide by the National Diabetes Information Clearinghouse, as well as through the Indian Health Service and through the state dental and diabetes control programs of the Centers for Disease Control. Also, in a government/industry cooperative effort, a company in the oral health care field is distributing the patient guide to dental offices and through the American Association of Diabetes Educators as part of the company's patient education program.

TMJ

Mr. Conte. What have been the recent developments in the research of TMJ (temporomandibular joint syndrome)?

Dr. Löe. Important longitudinal epidemiological studies supported by NIDR have shown that, for many individuals with pain or dysfunction in the jaw joint and muscles, these difficulties are self-limiting and episodic and do not become progressively worse. Nevertheless, some patients do suffer increasing, intense pain and progressive disability. Researchers have made substantial progress toward developing reliable, accurate methods for predicting which

TMD patients are particularly likely to develop progressive, severe jaw pain.

Research on new diagnostic techniques, such as magnetic resonance imaging and muscle spectroscopy, is rapidly improving our capability to detect structural and functional changes in the temporomandibular joint and the masticatory muscles, and to utilize this information in identifying underlying pathophysiological conditions producing jaw pain.

We are also supporting research on the treatment of individuals afflicted with TMJ disorders. For those patients with persistent jaw muscle tension and pain, but few indications of structural jaw joint defects, brief regimens of low doses of antidepressants often produce marked pain relief. Interestingly, this pain relief appears to relate to factors other than mood change per se. Scientists are evaluating whether the antidepressant regimens may work through changing patterns of nocturnal bruxism (tooth-grinding), which leave the jaw muscles sore and fatigued upon awakening. Investigators have recently reported that use of antidepressant regimens with mildly depressed TMD patients also results in their responding much more rapidly and with greater immediate, and long-term, benefit to biofeedback training. During such training, immediate auditory and visual feedback from psychophysiological monitoring devices allows patients to learn how they can control tension in their masticatory muscles and eliminate pain.

For those patients with joint pathology, some promising new techniques involving arthroscopy and lavage ("flooding" of the joint with a fluid) show the potential to produce positive results rivaling surgical interventions, with considerably less expense and fewer risks.

DENTAL RESEARCH TRAINING

Mr. Conte. What is the current situation in regard to the supply of dental scientists?

Dr. Löe. We are experiencing a shortage in the supply of dental scientists who are well-trained in the research areas related to the broadened clinical mission of the dental profession. In addition to dental caries and periodontal diseases, the nondental health problems in the orofacial region that dental scientists now have to address include pain, taste and smell disorders, mucosal ulcerations and infections, salivary disorders, oral cancer, and many manifestations of systemic disease. Work in such areas requires a wide spectrum of molecular, biochemical, and immunological experimental approaches. However, there is not only a shortage in the number of well-trained clinical dental scientists, but also a maldistribution among existing institutions. This is indicated by the fact that three-fourths of NIDR extramural awards go to one-third of the U.S. dental institutions. Thus there is also a need to assist those schools that currently may not have the necessary manpower base to develop an active dental research program.

Mr. Conte. In what areas of dental research is the need for investigators most pressing?

Dr. Löe. The Institute's mission is expanding from a primary emphasis on dental caries and periodontal diseases to investigation of all problems in the orofacial region. As a result, there is a pressing need to train dental research scholars who are competent to apply experimental techniques from molecular and cell biology, immunology, virology, biomaterials science, and computer science to investigate such areas as: 1) precancerous oral lesions and oral cancer; 2) oral complications in the medically compromised patient (e.g., the elderly, AIDS patients, diabetics, and people undergoing various oncologic and immunosupressive therapies); 3) disorders of smell and taste; 4) orofacial reconstruction (e.g., post-cancer surgery patients and post-traumatic injury patients); and 5) genetic diseases of bone and connective tissue and congenital malformations (e.g., "orphan diseases" such as ectodermal dysplasia, osteogenesis imperfecta, scleroderma, and orofacial clefts).

ORAL COMPLICATIONS OF CANCER THERAPY

Mr. Conte. Your opening statement said that the oral complications of cancer therapy is a top priority for your Institute. What are some of the oral complications involved?

Dr. Löe. Oral complications are associated with surgical, chemotherapeutic, radiation, and combined modality treatments for cancer. Complications are both acute and chronic, occur with therapies for non-head and neck cancers, and may have a significant impact on treatment. Oral complications can affect morbidity, the patient's tolerance of treatment, and the quality of life. In fact, death can sometimes result from severe oral complications.

As many as 400,000 patients a year develop oral complications of their cancer therapy. The most common complications are mucositis, local or systemic infection, and hemorrhage. Other oral complications include growth and developmental abnormalities, xerostomia and salivary gland dysfunction, rampant dental caries, taste loss, osteoradionecrosis, dermatitis, and trismus.

Mr. Conte. What is the current role for pre-therapy interventions in reducing the occurrence of oral complications in the cancer patient?

Dr. Löe. Appropriate pre-therapy interventions can significantly lessen morbidity and possibly decrease mortality associated with oral complications of cancer therapies. There is evidence that pre-existing oral disease unrelated to cancer or therapy may increase the risk of oral complications. Before the initiation of cancer therapy, a comprehensive pre-treatment dental evaluation is mandated. Other pre-treatment strategies include treatment of pre-existing dental disease, patient and family education and counseling, prevention of oral mucosal infections, interventions to modify salivary gland dysfunction, reduction of iatrogenic and disease-related neutropenia, and prevention of mucositis.

Mr. Conte. What are the directions for future research in this field?

Dr. Löe. According to recommendations made at the 1989 consensus development conference entitled "Oral Complications of Cancer Surgery," future directions for research include:

- Determine incidence and prevalence of oral complications related to different types of anticancer therapies and related risk factors.
- Study the mechanisms of cancer treatment injury to the hard and soft oral tissues at the molecular and cellular level and determine how these affect the oral environment.
- Develop radioprotective and chemoprotective agents in cancer treatment.
- Define and further document through prospective studies the effectiveness of initiating current pre-treatment oral care procedures on the incidence, severity, and extent of oral complications of cancer management.
- Conduct controlled studies to determine and test optimal antifungal, antiviral, and antibacterial therapies.
- Determine whether oral markers can serve as a predictor of problems of other organs.

ORAL COMPLICATIONS OF CANCER THERAPY

Mr. Roybal. What, if any, are the oral complications of cancer treatments?

Dr. Löe. Cancer treatment includes both chemotherapy and radiotherapy. These two approaches may be employed individually or in combination. The side effects that they induce include direct effects on the exposed tissues as well as indirect effects resulting from immunosuppression.

Oral problems resulting from chemotherapy include candidiasis, herpesvirus lesions, and bacterial infections. Mucositis (inflammation of the mucosal tissue forming the lips, tongue, and lining of the mouth) occurs in many patients treated for leukemia as well. Hemorrhage also results from the reduction of some vital blood-clotting factors and/or mechanisms.

Radiation effects resulting from treatment for cancer include xerostomia (dry mouth) as a result of damage to the salivary glands, radiation caries, radiation mucositis, taste loss, radiation-induced trismus, bone necrosis, and radiation-related malnutrition.

Mr. Roybal. Can anything be done to prevent these complications?

Dr. Löe. Prior to cancer treatment, the use of antibacterial, antiviral, and antifungal agents, particularly chlorhexidine, help to minimize selected oral complications of cancer treatment. In addition, a complete oral examination followed by aggressive prophylactic treatment including endodontic therapy and topical fluoride application have also proved beneficial. Anti-immunosuppressive pretreatment has been utilized for patients undergoing bone marrow transplant as well as for treatment for cancer patients.

RECONSTRUCTIVE SURGERY

Mr. Roybal. While at the dental school at UCLA, I observed reconstructive work being done on patients with oral cancer. Is there any research being funded in this particular area of surgery?

Dr. Löe. Yes; investigators at UCLA and several other institutions are developing surgical procedures to improve reconstruction of the jaws and face following cancer surgery and traumatic accidents. In fact, many of the clinical studies on correction of functionally and psychologically debilitating facial birth defects have direct impact for cancer reconstructive surgery.

Recent research efforts include: evaluation of new methods of immobilizing sections of jaw bone until surgical fractures have healed; development of procedures for moving sections of the upper and lower jaw in three dimensions; and evaluation of methods for grafting bone to replace that lost to surgery or missing due to a congenital defect. More basic studies, conducted in both intramural and extramural laboratories, have isolated factors that will induce the formation of entirely new bone, when implanted into areas of tissue where bone is missing due to a fracture or surgery.

Mr. Roybal. Is there a need to expand research in the area of reconstructive surgery for patients with oral cancer?

Dr. Löe. We believe that expansion is warranted. For example, new research efforts should be designed to minimize oral surgery and to coordinate reconstructive surgery with the construction and appropriate placement of prosthetic devices to restore optimal functioning of oral facial structures. There is a further need to improve methods of early diagnosis of oral cancer to minimize the necessity for radical cancer surgery, which often requires massive reconstruction of the orofacial complex.

Mr. Roybal. What about clinical research on surgical techniques or basic research on the types of materials needed to improve the care of these patients?

Dr. Löe. Further research is needed to develop materials necessary for the construction and development of prostheses to replace missing parts of the face resulting from cancer surgery. In addition, research is needed to identify and characterize biological factors that will generate natural growth and development of hard and soft tissues compromised as a result of surgical intervention.

NEW FINDINGS IN AIDS RESEARCH

Mr. Roybal. What new findings has dental research discovered about the AIDS virus?

Dr. Löe. Preliminary evidence from several investigators shows that saliva obtained from normal healthy volunteers inhibits the ability of HIV to infect peripheral blood lymphocytes in tissue culture. The responsible factors have not been definitively characterized with respect to size, molecular weight, chemical composition, or origin. The mechanisms by which the factors exert their inhibitory effect also have not been determined. To capitalize on these preliminary findings, the NIDR last year issued a request for applications entitled "Human Immunodeficiency Virus Inhibitory Factors in Human Saliva." A number of proposals were received in response to the request, and we anticipate funding the most meritorious of these this fiscal year.

Preliminary data from another investigation show that secretory leukocyte protease inhibitor (SLPI), a substance found in normal saliva and in nasal and bronchial secretions, possesses antiviral activity. Specifically, SLPI produced from parotid glands by recombinant technology clearly inhibits infection of cell cultures both by HIV and by a virulent strain of simian immunodeficiency virus. The SLPI protein inhibits infection by preventing the virus from entering the susceptible cells. The SLPI protein has undergone toxicity tests, and scientists are planning to conduct efficacy testing in animals soon.

Other recent findings include the detection of actual HIV in the gingival crevicular fluid (GCF) of nearly all subjects who had positive tests for HIV antibody in the blood. The virus was present in the GCF of some patients up to 6 months before these patients developed antibody in the blood. This early detection of the virus may permit earlier diagnosis of HIV infection and facilitate the application of preventive measures. Since gingival crevice fluid is readily accessible, this method may become especially appropriate for large populations in developing countries.

Hairy leukoplakia (HL) is second only to oral candidiasis in prevalence among oral opportunistic infections of AIDS patients and is generally accepted as conclusive evidence for the definitive diagnosis for AIDS. Epstein-Barr virus (EBV), a member of the herpesvirus family, has consistently been demonstrated to be localized in HL lesions. Further study is needed to determine the precise mechanism involved in the pathogenesis of the EBV/HL interaction. However, because the HL lesion responds favorably to treatment with acyclovir, these results suggest that antiviral agents may have potential for the treatment of some opportunistic lesions observed in HIV-infected patients.

In basic research, investigators continue to explore the role of certain white blood cells (monocytes), which are weakened but not killed by HIV. When infected by the virus, these cells undergo premature differentiation, which limits their ability to respond to normal immunologic stimuli. Work on HIV surface structure aimed at the design of anti-AIDS drugs or vaccines continues, along with new studies incorporating parts of the HIV genome in transgenic mice. These experimental animals are creating models for studying the role of specific HIV genes in disease progression as well as in the expression of specific symptoms, as in HIV-associated kidney disease.

ORAL HEALTH PROBLEMS OF MINORITIES

Mr. Roybal. Are there any studies proposed that would help identify the special oral health problems of minority groups?

Dr. Löe. In response to the information needs of various racial and ethnic minority groups, we have undertaken a number of national general population surveys of children and adults that have included attention to the oral health status of blacks and Hispanics. We have also participated in several surveys of the National Center for Health Statistics by designing, monitoring, and underwriting the costs for oral examination components of the 1971-74 National Health and Nutrition Examination Survey (NHANES-I), the Hispanic Health and Nutrition Examination Survey (H-HANES), and the 1988-1994 National Health and Nutrition Examination Survey (NHANES-III). Analyses of these latter national health surveys will not only provide important information about the oral health of minorities, which has previously been unavailable, but will be able to do so in the context of their overall general health status.

We are also currently collaborating and providing consultation to staff from the Indian Health Service with regard to the development of clinical trials of alternative periodontal treatment approaches, and have begun to explore the feasibility of studies of subpopulations at high-risk for dental caries.

A comprehensive review of what is currently known about the oral health characteristics of racial and ethnic minorities is also under way, which will include a critical analysis of extant literature, as well as the tabulation of new data from available national surveys, which have included some attention to key aspects of the oral health of racial and ethnic minorities in the United States.

Finally, concept clearance has recently been obtained to proceed with a major planning effort of special epidemiologic initiatives focused on the oral health of black Americans. Central to this latter effort will be the design of a prototype baseline survey of the oral health of black Americans in the context of an overall epidemiologic research program.

LONG-RANGE RESEARCH PLAN

Mr. Roybal. Previous mention was made of consulting and collaborating with minority and industry groups in the course of developing the new Long-Range Research Plan. What will be the role of these outside groups?

Dr. Löe. The Long-Range Research Plan for the Nineties emphasizes the need for broader collaborations with industry and minority groups to facilitate research and training efforts. With regard to industry, we plan to establish a liaison group consisting of industry representatives, extramural grantees, and NIDR staff. This group would meet from time to time to discuss research progress and review the potential for collaborations. The involvement of industry in support of long-term multicenter clinical trials would be especially valuable. Other kinds of collaborations could use industrial expertise in scaling up production of biochemicals, development of devices and new diagnostics, etc.

With regard to minorities, our plans for the 1990's emphasize the need to document the oral health status of various ethnic and minority groups. We want to enlist the aid of minority leaders and professional groups in planning and conducting these studies, and in subsequent research aimed at improving the oral health of these groups. Furthermore, we intend to increase efforts to recruit minority members into oral health research, beginning at the high school level and continuing on to college and post-graduate education and research training programs.

SPECIAL CARE PATIENTS

Mr. Stokes. I know that NIDR has a new initiative concerning patients who need special care. Are there some diseases or disorders that have a greater impact on minorities? Will you be addressing these conditions?

Dr. Löe. We know that some diseases and disorders are more prevalent among different ethnic and racial minorities and have taken those facts into consideration in our research efforts. For example, we are studying periodontal disease, a complication of diabetes, among the Pima Indians where the prevalence of adult-onset diabetes is the highest in the world. Diabetes, hypertension, oral cancers, HIV infection, and drug-related birth defects are also examples of diseases and disorders that affect minority groups disproportionately. In some cases the impact of disease is greater in some individuals or groups because of socioeconomic reasons; in others there may be intrinsic differences in susceptibility.

An important goal of NIDR research in the 1990's will be to collaborate with ethnic and racial minority professional organizations to plan and carry out studies to determine oral health status and risk factors for disease. We can then develop appropriate preventive and treatment approaches targeted to these groups.

ORAL HEALTH STATUS AMONG MINORITIES

Mr. Stokes. In connection with your initiative on older Americans, what studies are you planning to undertake that would provide NIDR with information on the oral health status of minorities?

Dr. Löe. In recent years there have been numerous efforts to document the health status of black Americans. Most notable among these efforts, of course, have been the Secretary's Task Force Reports on Black and Other Minority Health. However, even a cursory review of these and other related efforts highlights the fact that available data on the oral health of black Americans are subject to a number of limitations, including insufficient sample sizes, limited coverage of the black population, selected problems with the reliability and validity of measurements, limited scope of measurement of oral diseases and conditions, and lack of indepth contextual information. Clearly, there is a serious need for a comprehensive assessment of the oral health of black Americans.

We hope to fund a major new project that would address these concerns. As in other planning efforts of this kind, specific attention would be given to the following: 1) the formulation of major questions that most need to be answered about the oral health of black Americans; 2) evaluation of the adequacy of existing data bases to answer these questions; 3) identification of major data gaps for which new data collection efforts are required; 4) the outlining of a program of research (including baseline and follow-up surveys, clinical trials, demonstration projects, secondary analyses, and other studies), which together would provide the comprehensive and systematic epidemiologic information needed to fill these gaps; 5) the development of a detailed design for a comprehensive baseline survey of the oral health of black Americans; and 6) the development of cost estimates both for this latter baseline survey, and for other projects included in the outline of a program of research in this area.

ANIMALS IN RESEARCH

Mr. Stokes. I understand that NIDR has developed methods that will reduce dramatically the need for animals in caries (cavities) research. Can you tell us more about these methods?

Dr. Löe. Our investigators have developed safe, short-term, intraoral methods that reduce dramatically the need for animals in caries research. Appliances containing samples of tooth surfaces placed in the mouth show that the production of acids that can dissolve tooth enamel by caries-promoting foods can be decreased by supplementing the diet with foods known to stimulate saliva flow and/or prevent acid accumulation in dental plaque. We have also used these methods to test various fluoride regimens for their effectiveness in preventing caries or restoring tooth enamel after acid attack. These studies should lead to the "ideal" mouthrinse to prevent dental caries in high-risk populations.

ARTIFICIAL SALIVA

Mr. Stokes. Is artificial saliva currently available? If not, how soon might we see it?

Dr. Löe. Although artificial salivas are currently available, they are poor substitutes. Saliva has many roles in protecting the mouth, which can be categorized in three basic ways: protecting teeth, protecting the soft tissues, and controlling microbial infections. Currently available artificial salivas do an adequate job of protecting the teeth but have no real beneficial effects on the remaining two functions. Thus, people with malfunctioning salivary glands often complain of oral dryness, the fragility of their oral soft tissues, and difficulty swallowing dry foods; additionally, they show signs of oral fungal infection.

The Institute has sponsored, and continues to sponsor, considerable study of the specific salivary proteins that subserve these particular protective roles. By characterizing these salivary proteins, we have begun to learn which parts of the protein molecules actually are the key functional elements. Efforts are now under way to develop the means to make these elements and deliver them in a useful manner to the mouth to provide soft tissue protection and antimicrobial benefits. It is difficult to predict when these may be available for clinical testing, but it could possibly occur within this decade.

TASTE AND SMELL

Mr. Stokes. To what extent do the senses of taste and smell diminish with aging?

Dr. Löe. Among generally healthy persons, the sense of taste changes little with increased age except, perhaps, in the case of denture wearers who often report taste complaints. On the other hand, there do appear to be decrements in olfaction in the course of normal aging. Objective studies conducted by NIDR staff show that any reductions in the ability to taste with increased age are very modest and taste-quality specific (sweet, sour, salty, or bitter). Nonetheless, many healthy older people do complain about reduced food enjoyment. It appears that these complaints are most attributable to reductions in the ability to smell.

PAIN RESEARCH

Mr. Stokes. I understand that you support some of the most significant pain research being conducted in this country and that your Institute is the lead Institute for pain research at NIH. Can you tell me more about your work in this area?

Dr. Löe. The NIDR continues its historic role as the leading pain research Institute at the NIH. Moreover, the Institute has an international reputation as the site of one of the world's best pain research laboratories. Dr. Ronald Dubner, chief of NIDR's Neurobiology and Anesthesiology Branch (NAB), recently received the Bristol-Meyers Award for Distinguished Achievement in Pain Research in recognition of his contributions and leadership in this area.

Our NAB provides the leadership and coordinates the activities of the NIDR/NIH Pain Research Clinic. Both basic and clinical research on acute and chronic pain are performed at the Pain Clinic. Improved methods for the control of acute and postoperative pain are being developed; these will benefit both dental and general surgical practice. Basic research into the causes of postoperative pain has greatly expanded our knowledge of the biochemical mediators of the pain that accompanies inflammation, and the identification of these mediators has suggested several new pharmacological strategies for the alleviation of postoperative pain.

The NIDR extramural program also supports basic and clinical research to develop the means to prevent or relieve acute dental pain, such as that occurring following oral surgery or when teeth are drilled. Major strides have already been made in expanding understanding of the structures and processes underlying transmission and control of acute pain in the teeth and face, and in developing improved pharmacological and nonpharmacological methods for safely and effectively reducing acute pain. Chronic pain appears to differ in many significant ways and currently presents a more daunting scientific and clinical challenge to dental science and dental practice.

Improvements in analgesic therapy are predicated upon our ability to measure pain accurately. The NAB has an active program for the development of better pain measurement techniques. In addition, intramural scientists at the Pain Clinic are investigating the causes and treatment of neuropathic pain syndromes (associated with nerve injury). For example, the incidence of a very painful condition, post-herpetic neuropathy (residual pain following an attack of shingles), is increasing due to aging of the population. We have recently shown that amitriptyline, a drug generally used for the treatment of depression, effectively suppresses the pain of post-herpetic neuropathy.

The NAB also supports laboratories that conduct basic research into the fundamental mechanisms of pain perception and its control; this basic research is the foundation for our work toward the control of pain. Our scientists have recently developed models of peripheral tissue inflammation and nerve injury in order to study the responses of the nervous system to the pain caused by these conditions. Several new discoveries have come from the use of these models. For example, we have found that the production of dynorphin, a naturally occurring biochemical with an action like morphine, is greatly increased in spinal cord nerve cells when pain arising from tissue injury or neuropathy is present. It is possible that this response is part of the body's own defenses against pain.

Current extramural research suggests that clinical patients with chronic orofacial pain may show deficiencies in their capability to produce neurochemical substances that act as natural "opiates" under conditions of stress. Other NIDR-supported neuroscientists have shown that trigeminal nerve injury can result in significant changes in the responsivity of central neurons, including their "firing" when previously innocuous stimuli are presented peripherally and responding to stimulation in a much wider area than before. These changes correspond to some of the clinical characteristics of severe chronic pain conditions, such as trigeminal neuralgias, seen in the elderly.

SPECIAL CARE PATIENTS

Mr. Early. Your statement highlights an initiative related to "special care" patients and that their health problems are increasingly under research attack by NIDR scientists. What are your FY 1991 plans with regard to this initiative?

Dr. Löe. We intend to increase research on the range of diseases and handicapping conditions that characterize special care patients, using such mechanisms as requests for applications and program announcements. Currently, we have announcements to encourage research in such areas as temporomandibular joint disorders and problems of taste and smell. From our three craniofacial biology research centers, we expect to see expanded research on genetic and congenital conditions affecting the head and mouth. Both our extramural and intramural research programs include important research on diseases such as Sjögren's syndrome, osteogenesis imperfecta, and oral cancer. We are also working closely with a newly formed coalition of health voluntary organizations representing patients with conditions that compromise oral health. These groups are a valuable resource, providing tissue samples or patient volunteers for clinical studies.

Mr. Early. How much is included in your FY 1991 budget request for this purpose?

Dr. Löe. Because of the overlapping nature of the individual projects, it is difficult to provide a specific dollar amount for this initiative. Its importance in improving the oral health and quality of life for special groups in the American population has prompted us to redirect funds as necessary within the NIDR budget.

Mr. Early. What progress are your researchers making in attacking this area?

Dr. Löe. The following are a few examples of recent progress:

- Development of a drug treatment for Sjögren's syndrome that helps to relieve the dry mouth associated with this condition. Other research is aimed at elucidating the immune system defect that leads to the destruction of salivary and tear glands.

- Development of an animal model to study the role of a certain growth factor in oral cancers. These studies have recently been extended to human subjects in which the factor, transforming growth factor-alpha, was found to be present in all human oral cancers examined.

- Clinical trial of the use of permanent dental implants instead of removable dentures in young, still growing patients with ectodermal dysplasia, a genetic disease associated with malformed or missing teeth.

- Clinical studies of bone diseases, such as osteogenesis imperfecta (OI) and osteopetrosis (OP), aimed at understanding the cellular defects resulting from defective genes. In particular, NIDR scientists are analyzing bone cell samples from OI patients to determine the nature of the collagen and other bone protein abnormalities seen in these patients. In the case of OP, researchers have developed an animal model to study the relation of specific immune system defects to the defects in bone resorption seen in this condition.

LONG-RANGE RESEARCH PLAN

Mr. Early. Dr. Löe, would you summarize the major recommendations of the Institute's new Long-Range Research Plan?

Dr. Löe. The plan encompasses some 75 major recommendations in over 20 different areas, ranging from AIDS to xerostomia (or dry mouth). We can, however, summarize those recommendations in three broad categories:

- An emphasis on research to resolve the oral health problems of special care patients--individuals with disease, handicapping conditions, or disease treatments that compromise oral health. Such conditions include "orphan" diseases such as scleroderma and ectodermal dysplasia, as well as highly prevalent diseases such as diabetes and cancer. In the case of cancer patients, we are concerned with the prevention and treatment of oral cancers, as well as the amelioration of the oral health problems that can occur as a result of cancer treatments such as radiation and chemotherapy.

- An emphasis on adults and older Americans, with the goal of eliminating tooth loss and preventing further deterioration in the oral health of people who have already experienced extensive disease. These are the aims of our Research and Action Program described in our report to the Committee in December 1988. We will need to determine which individuals are at high risk for oral health problems, whether because of health or socioeconomic factors. We expect to expand epidemiologic research, particularly looking at racial and ethnic minorities, homebound and institutionalized elderly, and other little-studied populations where we suspect the needs are greatest and will require innovative approaches to prevention and treatment.

- An emphasis on research that will enable us to get on with the task of essentially eliminating the two major dental diseases--caries and periodontal diseases. For all the evidence that these diseases have been declining in prevalence and severity, we must reckon with the fact that half the schoolchildren in America still have cavities and that periodontal diseases affect the majority of adults, increasing in severity with age. Better means of early diagnosis, easier means of self-care, and improved professional methods of prevention, treatment, and even reversal of disease are among the goals of this research.

Mr. Early. Are any of these recommendations incorporated in your research program for FY 1991? Are funds included for this purpose?

Dr. Löe. Our research program for FY 1991 incorporates all these recommendations, and the request includes funds for a beginning effort in their achievement.

PERCENTILES AND AWARD RATES

Mr. Early. What will be NIDR's payline percentile for FY 1991, and how does this compare with FY 1990 and FY 1989?

Dr. Löe. We anticipate that we would be able to pay through the 14th percentile at the FY 1991 request level, compared to our estimate of the 12th percentile in FY 1990 and to the 24th percentile in FY 1989.

Mr. Early. What are you projecting for an award rate under the FY 1991 budget request? How does this compare with the award rates for FY 1990 and FY 1989?

Dr. Löe. The FY 1991 budget request would permit an award rate of approximately 21.5 percent, compared to an estimated 20.5 percent in FY 1990 and 26.6 percent in FY 1989.

EFFECT OF DECREASING NUMBERS OF GRANTS

Mr. Early. Doctor, NIDR will fund 103 new and competing awards in FY 1991. While this is somewhat of an increase over FY 1990, it is fewer than the NIDR has funded over the past several years. I also see that the total number of grants continues to decline. What effect will this have on the two initiatives you speak of in your statement?

Dr. Löe. The decline in grants may limit the range of research called for in our new initiatives. However, we do support both broad-based and categorical research centers, where investigators will be addressing many research issues relevant to our new initiatives.

DOWNWARD NEGOTIATIONS

Mr. Early. What is the level of downward negotiations for new and competing grants in FY 1991, and how does this compare to FY 1990 and FY 1989? What about noncompeting grants?

Dr. Löe. The downward negotiations for the 3-year period are as follows:

	New and Competing	Noncompeting
FY 1989 Actual............	10.6%	13.7%
FY 1990 Estimate..........	15%	12%
FY 1991 Request...........	15%	12%

Mr. Early. What effect are these downward negotiations having on dental research?

Dr. Löe. It is my professional opinion that downward negotiations of this magnitude could lead to disruptions in the investigators' ability to perform the approved research. While investigators with larger grants, such as program project grants, might be able to accomplish essential functions by rebudgeting within available funds, most investigators would need to reduce support and professional staffs and to forego expenditures for some equipment, supplies, travel, and patient and animal work. These limitations could disrupt the grantees' ability to accomplish research goals and thus impede scientific progress of the projects. While these sequelae could be minimized by not negotiating so drastically on individual grants, the alternative choice of funding fewer grants in the aggregate could similarly limit advances in dental sciences and knowledge.

Mr. Early. You plan to support the same number of centers (21) in FY 1990 and FY 1991 with no increase in funding. I assume this means there will be downward negotiations in NIDR's centers program? If so, what will the percentage be for noncompeting and for competing centers?

Dr. Löe. Downward negotiations of over 16 percent would be necessary at the FY 1991 request level for noncompeting and competing research centers.

Mr. Early. How does this compare with FY 1990 and FY 1989?

Dr. Löe. In FY 1990, a 15-percent downward negotiation rate is anticipated; the actual rate for FY 1989 was 10 percent.

Mr. Early. What effect is this having on research conducted at these centers?

Dr. Löe. The effect on research conducted at the centers is essentially that described above in response to the question on the effect of downward negotiations on research project grants.

RESEARCH CENTERS

Mr. Early. Do you have a problem similar to the NHLBI's regarding centers as the primary mechanism for supporting clinical research?

Dr. Löe. At the present time, we do not have a similar problem in that our clinical research is conducted principally through R&D contracts, research project grants, and the intramural research program. However, later this fiscal year we will be making the awards for two new dental clinical research core centers. When these centers are established, we will be supporting a substantial level of clinical research through the centers mechanism and thus could begin to experience problems such as those being expressed by NHLBI.

Mr. Early. Doctor, over the past few years, the NIDR has revamped its centers program. Have downward negotiations created difficulties in your Institute's ability to establish and properly fund new or revamped centers?

Dr. Löe. The same downward negotiation rate is being applied to each center equally. In FY 1990 each center, regardless of type, is being reduced by 15 percent; the reduction at the FY 1991 request level would be over 16 percent for each center.

The individual center directors have been given complete flexibility in how the reductions will be applied in order to minimize the impact. The approaches have varied from uniform reductions in each of the center projects to the elimination of entire projects. Obviously, the pace of the research has been slowed as a result of the reductions, and the grantees have expressed concern about the amount of progress expected when the centers are competitively reviewed.

Mr. Early. Doctor Löe, what are NIDR's plans for establishing Dental Clinical Core Research Centers? How much is included in your budget request for these centers?

Dr. Löe. Last fall, we issued a Request for Applications (RFA) for these new centers. Responses to that RFA are expected in March 1990. Depending on the outcome of the peer review process, we anticipate the award of two core centers later this fiscal year. Approximately $1.3 million is included in the FY 1990 appropriation for these centers; this would drop to about $1.2 million at the FY 1991 request level.

CLINICAL TRIALS

Mr. Early. Will you be funding any new clinical trials in FY 1991? If so, please provide a list of these for the record.

Dr. Löe. No major new clinical trials would be possible within the FY 1991 budget request.

Mr. Early. Are there any new clinical trials ready to go for which the FY 1991 budget request does not include funds? If so, provide a list of these, along with a brief description, the first year cost, and the total cost of the trial.

Dr. Löe. The following major new clinical trials could begin in FY 1991 if funds were available:

	First year cost ($000)	Total projected cost ($000)
Evaluation of exposure to fluoride in non-fluoridated communities	$500	$1,000
Evaluation of various modalities for preventing caries, improving periodontal health, retaining permanent teeth, and practicing self-care in "special patient" populations (e.g., diabetes, cystic fibrosis, lupus)	1,500	6,000

	First year cost ($000)	Total projected cost ($000)
Evaluation of various modalities for preventing caries, improving periodontal health, retaining permanent teeth, and practicing self-care in patients with "orphan diseases" (e.g., scleroderma, osteogenesis and dentinogenesis imperfecta, ectodermal dysplasias, and Sjögren's syndrome)	$1,500	$6,000
Evaluating new clinical approaches to treating the loss of alveolar bone and of periodontal attachment through guided tissue regeneration and osteogenin	1,500	5,000
Prevention and reduction of oral complications from cancer chemotherapy and radiation	1,000	3,000
Evaluating the effects of various treatments to suppress recurrence of herpesvirus	1,000	3,000
Effect of drug pretreatment of individuals at risk for oral cancer	500	1,500
Effects of drug therapy on recurrent oral cancer	500	3,000
Clinical evaluation of sealants, xylitol, chlorhexidine, and various fluoride modalities for caries prevention in high-risk populations	1,500	3,000
Multi-institutional clinical trial of single- and multi-tooth dental implants	1,500	6,000
Evaluation of criteria for replacement of dental restorations	400	2,000
Analgesic and biochemical responses to peripheral opiates in patients with dental pain	150	300
Evaluating noninvasive treatment for temporomandibular disorders (TMD)	750	2,500
Rehabilitation of dysphagic patients	500	2,000
Effect of periodontal treatment on insulin requirements of patients with diabetic periodontitis	500	1,500
Assessment of new dental biomaterials (e.g., bonding materials, dental cement, and root canal materials)	1,000	3,000
Orthognathic surgery clinical trials	600	2,400

	First year cost ($000)	Total projected cost ($000)
Evaluation of various prostheses for orofacial reconstruction	$500	$2,000
Evaluation of the use of genetic probes of gingival crevicular fluid for the early detection of HIV infection	750	2,200
Salivary gland secretions in HIV infection	250	250
Evaluation of mucosal biopsies from AIDS patients for candidiasis	250	750
Salivary and intestinal fluid IgA response in patients with AIDS	300	900
Development and testing of methods to be used for epidemiological studies of human papillomaviruses in the oral cavity	100	200
Total	17,050	57,500

MATERIALS SCIENCE RESEARCH CENTERS

Mr. Early. Do the new materials science research centers established by NIDR have particular focal points?

Dr. Löe. Scientists at the Specialized Materials Science Research Center at the University of Michigan are working on the development of new materials with elastic properties for use in extraoral maxillofacial prostheses and permanently soft denture liners. They also are creating new polymer-ceramic composites with long-term wear resistance for use in tooth restorations as well as new laboratory methods to evaluate the aging of these composites in the oral environment. Another area of focus is the development of new ceramics for crowns and bridges that are esthetically pleasing and offer major improvements in toughness and fracture resistance. In other studies, investigators will conduct laboratory and animal tests that predict the short- and long-term biocompatibility of dental materials for applications ranging from implants to restorations.

The Specialized Materials Science Research Center at the University of Florida will focus on developing controlled-release polymer microsphere and microcapsule delivery systems for a broad spectrum of diagnostic and therapeutic agents; innovative restorative resins that deliver a controlled dose of fluoride or other therapeutic agent on demand without causing structural degradation over the projected lifetime of the restoration or appliance; new processes for producing bioactive glasses that form direct interfaces with tissue and promote wound healing in pulp and at the tooth apex; and a high-strength glass-ceramic system with chemical and thermal control of color. Current glass-ceramic formulations can only be shaded on the external surface, and the technique must sometimes be supplemented with the use of a pigmented cement agent.

The Center for Excellence for Materials Science Research at the National Institute of Standards and Technology has several research projects under way, including the development of a reinforcing material--a glass-ceramic that contains beta-quartz--that can strengthen composite restorations. Other studies are looking at ways to enhance the durability and marginal adaptability of dental composites through the use of newly developed monomers. Investigators at the center also are working on the development of a "synthetic dentin," new prosthetic materials and techniques, and novel materials that shield against attack by microorganisms by binding both to enamel and dentin.

Mr. Early. What kind of collaboration is there with the private sector?

Dr. Löe. The Specialized Materials Research Centers will allow for enhanced collaborative opportunities with the private sector. Extensive interactions with industrial companies is anticipated through development of new biomaterials. In addition, one center will further strengthen its relationship with industry through the establishment of a Restorative Materials Information Network. Among the network's functions is the production of a newsletter highlighting research accomplishments that will be distributed to dental manufacturers' research and development directors. Also, industry representatives will be invited to attend annual dental materials conferences sponsored by the center and present talks in conjunction with the Information Network's monthly seminar series.

INCREASE OVER BUDGET REQUEST

Mr. Early. If there is an increase over the FY 1991 budget request, how would NIDR use these funds?

Dr. Löe. Because of the importance of our two new initiatives--to address the needs of "special care" patients and to improve the oral health of adults and older Americans--our first priority would be to invest our funds in pursuit of these objectives. Both these programs will result in increased savings and improved quality of life.

The comprehensive nature of these initiatives spreads across all the funding mechanisms available to the Institute. Therefore, an increase over the 1991 budget request would be applied by mechanism as follows: restoration of full costs for all research grants, including centers; an increased award rate (ideally to 45-percent) for new and competing research project grants; the establishment of new research centers to meet the goal of 30 centers, as addressed in our report to Congress a few years ago; additional funding for minority research support; and enhancement of our manpower development programs.

AIDS

Mr. Dwyer. Dental research has played an important role in combatting the AIDS virus. Oral lesions are often a first indicator of HIV infection. In New Jersey, the University of Medicine and Dentistry operates a dental clinic in Newark, which treats the unique oral problems of AIDS sufferers. What is being done to train and educate dentists, dental students, and other oral health professionals about candidiasis and the other problems associated with HIV-infected individuals?

Dr. Löe. The education of oral health professionals has been a collaborative effort across federal and professional organizations. The NIDR has been part of these activities both domestically and internationally. Working with organizations such as the American Association of Dental Schools, the American Dental Association, the Department of Veterans Affairs, the Centers for Disease Control, the Food and Drug Administration, the Indian Health Service, the Health Resources and Services Administration, and other Institutes at the NIH, the NIDR has been active in supporting publications, symposia at national meetings, and curricula for dental professional schools and for continuing education courses on the oral problems associated with HIV-infected individuals.

Specifically, Dr. Preston A. Littleton, Jr., Deputy Director of the NIDR and Deputy Chief Dental Officer of the U.S. Public Health Service, coordinated the support for a special November 1989 Supplement to the Journal of the American Dental Association called "HIV: Beyond Infection Control." This supplement has been broadly circulated within and outside the dental profession and addresses key oral problems and their treatment.

NIDR staff also participated in the planning and implementation of the first conference on "Oral Manifestations of AIDS" held in 1988, focussing upon the diagnosis and management of HIV-associated infections. The proceedings of this conference have been widely distributed.

On the international side, the NIDR has been active since 1988 as part of the International Coordination Group on Oral Manifestations of HIV Infection together with the World Health Organization. One of the four main goal areas is called Health Education and Health Promotion. The NIDR has focussed its activities on epidemiology and surveillance. As part of that effort, NIDR is supporting, and staff are participating as faculty, in an international course to be held this year on oral health manifestations of AIDS. This course is under the direction of the University of California School of Public Health and is aimed at training dentists from developing countries.

The NIDR has been a key player in the education of dental professionals with regard to infection control. A video tape and manual documenting recommended practices has been developed and distributed as a result of efforts by the NIDR, the Department of

Veterans Affairs, the Food and Drug Administration, and the Centers for Disease Control.

Mr. Dwyer. Despite continued fears, no one to date has contracted AIDS by kissing an HIV-positive individual. Could you please discuss the role of saliva and the potential of an oral transmission of HIV?

Dr. Löe. HIV-1 can be recovered from the oral fluids. However, virus is found infrequently and in very small amounts. It is unclear whether the virus is from cells, blood, or saliva, all of which are in the mouth, or whether the virus isolated is infectious. Extensive epidemiologic studies argue that saliva and the oral cavity are not a route of transmission for HIV-1. Family studies of persons living with HIV-1-infected individuals, occupational studies of dentists and other health care workers, and sexual practice studies of HIV-1-infected persons all support the contention that HIV-1 is not transmitted orally. Kissing, sharing eating utensils, even sharing toothbrushes with an HIV-1-infected individual are seemingly safe. Recent research has failed to demonstrate transmission of HIV-1 between children even by biting.

Although HIV-1 may be found in saliva, saliva does not appear to support oral transmission of the virus. This may be explained, in part, by protective factors in saliva. Research at the NIDR has shown that saliva is capable of inhibiting the infectivity of HIV-1. This inhibitory activity was found in saliva from normal men, women, and children, as well as men who were infected with HIV-1. Further studies are under way to fully identify and characterize this activity.

TMJ-RELATED DISORDERS

Mr. Dwyer. As the sponsor of "National Jaw Joint and Temporomandibular Joint Disorder Week," I am very interested in basic and clinical research into TMJ and related disorders. What is the status of research into TMD?

Dr. Löe. The scope and quality of research on this topic is steadily improving. We intend to accelerate further progress through two program announcements encouraging research related to the etiology, epidemiology, diagnosis, and prevention of these conditions.

NIDR-supported scientists contributed many of the articles included in the March 1990 issue of the Journal of the American Dental Association, which was devoted entirely to the topic of temporomandibular disorders. NIDR-supported scientists and consultants recently played a key leadership role in developing a new organization, the Association of University TMJ and Facial Pain Programs, which is expected to help accelerate the development of consensus regarding optimal clinical management, provide an enhanced capability for dental schools to implement multi-site clinical trials, and to accelerate improvements in the training that dental schools provide regarding temporomandibular disorders.

Mr. Dwyer. What innovative treatments are being used to treat individuals afflicted with TMD?

Dr. Löe. For those patients with persistent jaw muscle tension and pain, but few indications of structural jaw joint defects, brief regimens of low doses of antidepressants often produce marked pain relief. Interestingly, this pain relief appears to relate to factors other than mood change per se. Scientists are evaluating whether the antidepressant regimens may work through changing patterns of nocturnal bruxism (tooth-grinding), which leave the jaw muscles sore and fatigued upon awakening. Investigators have recently reported that use of antidepressant regimens with mildly depressed TMD patients also results in their responding much more rapidly and with greater immediate, and long-term, benefit to biofeedback training. During such training, immediate auditory and visual feedback from psychophysiological monitoring devices allows patients to learn how they can control tension in their masticatory muscles and eliminate pain.

For those patients with joint pathology, some promising new techniques involving arthroscopy and lavage ("flooding" of the joint with a fluid) show the potential to produce positive results rivaling surgical interventions, with considerably less expense and fewer risks.

DENTAL CLINICAL RESEARCH CENTERS

Mr. Hoyer. There were funds in the FY 1990 appropriation for new dental clinical research centers. The NIDR has issued a Request for Applications for the establishment of these centers in October of last year. How many centers will the Institute fund and at what level?

Dr. Löe. Depending on the outcome of peer review, we anticipate awarding two dental clinical research core centers. The cost of these two new centers is estimated at $1.3 million for FY 1990.

Mr. Hoyer. How much is contained in the FY 1991 budget for the centers?

Dr. Löe. About $1.2 million would be available for the new core centers within the FY 1991 budget request.

Mr. Hoyer. What areas of investigation do you anticipate will be funded through the centers in FY 1990?

Dr. Löe. The intent of the clinical research core center grant is to expand and improve the clinical research capability and potential of the Nation's dental schools and dental research institutions. The core centers will provide the necessary environment to conduct clinical trials and studies and expedite the translation of new knowledge from the laboratory to the clinic and the testing of new agents and procedures for diagnosis, prevention, and treatment of oral and dental diseases and conditions. The "Research and Action Program for Improving the Oral Health of Adults and Older Americans" requires these types of facilities for conducting clinical studies involving older populations.

DENTIST SCIENTIST PROGRAM

Mr. Hoyer. The Dentist Scientist Program, which I have been especially interested in, was designed to prepare dentists for careers in oral health research. How many individuals will enter the program in 1990 and how many will graduate?

Dr. Löe. Approximately 16 to 18 individuals will enter the program in 1990 and an estimated 24 will graduate.

Mr. Hoyer. At what level is the program funded in FY 1990 and FY 1991?

Dr. Löe. We estimate that approximately $6.2 million will be obligated in this program in FY 1990 and FY 1991.

Mr. Hoyer. How is the program progressing generally?

Dr. Löe. The program is progressing very well. All the program directors remain extremely enthusiastic about the progress their dentist scientists are making, and they are in agreement that these individuals are the best and the brightest; their enthusiasm, hard work, and commitment is inspiring.

Mr. Hoyer. Do you know what the first class of graduates will do upon graduation?

Dr. Löe. The first graduates will all go into academia, into career ladder positions of research/teaching/clinical activity. First indications are that they will have a number of very good employment opportunities from which to choose.

Mr. Hoyer. Now that the program has reached "steady-state," are there any changes, improvements, or growth that you would recommend in your professional judgment?

Dr. Löe. One of the problems that we and the respective institutions are experiencing is that some of the dentist scientists who are pursuing certain clinical tracks (i.e., orthodontics and oral/maxillofacial surgery) will require more than the 5 years of support provided by NIDR. The institution is expected to provide the support for any additional time that may be required to complete the training process. This may become a heavy financial burden on those institutions.

In addition, we are concerned that, once these dentist scientists enter the academic arena and must compete for research grant support, those funds may not be available due to the current fiscal constraints. Some thought has been given to providing a "bridge grant" for which only those newly minted graduates would compete. This "bridge grant" might be in the form of a small grant, on the order of $30,000 to $50,000, for 3 to 5 years.

CLINICAL TRIALS

Mr. Hoyer. I know that clinical trials are an important component of research in the field of oral health. Are there any major trials that you plan for FY 1990 or 1991, or that you would like to undertake, if you had sufficient funds?

Dr. Löe. No new major clinical trials can be undertaken within the level provided by the FY 1990 appropriation or within the FY 1991 request. We have identified 23 major new clinical trials, at a first-year cost of approximately $17 million, that could be undertaken if funds were available:

	First year cost ($000)	Total projected cost ($000)
Evaluation of exposure to fluoride in non-fluoridated communities	$500	$1,000
Evaluation of various modalities for preventing caries, improving periodontal health, retaining permanent teeth, and practicing self-care in "special patient" populations (e.g., diabetes, cystic fibrosis, lupus)	1,500	6,000

	First year cost ($000)	Total projected cost ($000)
Evaluation of various modalities for preventing caries, improving periodontal health, retaining permanent teeth, and practicing self-care in patients with "orphan diseases" (e.g., scleroderma, osteogenesis and dentinogenesis imperfecta, ectodermal dysplasias, and Sjögren's syndrome)	$1,500	$6,000
Evaluating new clinical approaches to treating the loss of alveolar bone and of periodontal attachment through guided tissue regeneration and osteogenin	1,500	5,000
Prevention and reduction of oral complications from cancer chemotherapy and radiation	1,000	3,000
Evaluating the effects of various treatments to suppress recurrence of herpesvirus	1,000	3,000
Effect of drug pretreatment of individuals at risk for oral cancer	500	1,500
Effects of drug therapy on recurrent oral cancer	500	3,000
Clinical evaluation of sealants, xylitol, chlorhexidine, and various fluoride modalities for caries prevention in high-risk populations	1,500	3,000
Multi-institutional clinical trial of single- and multi-tooth dental implants	1,500	6,000
Evaluation of criteria for replacement of dental restorations	400	2,000
Analgesic and biochemical responses to peripheral opiates in patients with dental pain	150	300
Evaluating noninvasive treatment for temporomandibular disorders (TMD)	750	2,500
Rehabilitation of dysphagic patients	500	2,000
Effect of periodontal treatment on insulin requirements of patients with diabetic periodontitis	500	1,500
Assessment of new dental biomaterials (e.g., bonding materials, dental cement, and root canal materials)	1,000	3,000
Orthognathic surgery clinical trials	600	2,400

	First year cost ($000)	Total projected cost ($000)
Evaluation of various prostheses for orofacial reconstruction	$500	$2,000
Evaluation of the use of genetic probes of gingival crevicular fluid for the early detection of HIV infection	750	2,200
Salivary gland secretions in HIV infection	250	250
Evaluation of mucosal biopsies from AIDS patients for candidiasis	250	750
Salivary and intestinal fluid IgA response in patients with AIDS	300	900
Development and testing of methods to be used for epidemiological studies of human papillomaviruses in the oral cavity	100	200
Total	17,050	57,500

AIDS

Mr. Hoyer. What will be the focus of NIDR research on HIV for FY 1990 in the areas of detecting the infection and inhibiting its spread?

Dr. Löe. The NIDR will continue to support and conduct research on the oral manifestations associated with HIV infection and on the role of saliva in the transmission or inhibition of HIV and other pathogenic organisms. Research grants will range from basic laboratory studies on the molecular biology of the opportunistic fungus _Candida albicans_ to epidemiologic studies of large cohorts of individuals at risk for HIV, who are being examined for opportunistic oral lesions and tested to determine sero-status.

Since the role of saliva in HIV infection has not been fully clarified, studies will be devoted to the role of saliva in transmission or inhibition of HIV infectivity. Investigators will also explore the potential antiviral properties of saliva against various members of the herpesvirus family: herpes simplex virus, Epstein-Barr virus, and cytomegalovirus--all of which have been detected in oral lesions of AIDS patients. The possibility of using fluid leaking from the gums at sites of periodontal disease to detect the presence of HIV will continue to be explored. Preliminary studies indicate that HIV can be recovered from this fluid early in the course of infection, even before an antibody response has been mounted.

The concentrations of relevant salivary constituents will be determined in the salivas of normal controls and immunologically compromised HIV-infected patients. The data obtained could contribute to the understanding of the in vivo pathogenesis of recurrent herpesvirus infections in patients without AIDS and provide new insight into the protective mechanisms of saliva in individuals with other types of severe immunodeficiencies.

Our collaborative project with the Walter Reed Army Institute of Research will continue. This study is documenting AIDS-related oral changes with disease progression, changes in oral ecology, and effective treatment of oral conditions.

ORAL HEALTH AND OTHER DISEASE

Mr. Hoyer. Could you comment on how poor dental health interferes with proper treatment of patients suffering from major diseases?

Dr. Löe. Since the tissues of the mouth are connected with the rest of the body, an individual whose general health is jeopardized by systemic disease may experience further complications because of oral health problems. We see this in the case of people scheduled for prosthetic operations to replace defective heart valves or hip joints, for example, or individuals who are candidates for organ or bone marrow transplants who receive immunosuppressive drugs. It is essential that these patients have any oral problems taken care of before undergoing surgery to prevent the transmission of oral bacteria or other infectious agents to the sites of the prothesis or tissues involved in the surgery.

In the case of diseases associated with weakened immunity, such as AIDS, it is also important to maintain good oral health. Not only are oral diseases common complications of infection with HIV, but there is also a risk that these infections can spread to the respiratory or intestinal systems or gain access to the bloodstream if they are not promptly and effectively treated.

Diabetes is another systemic disease that may be worsened by poor oral health. Periodontal disease is considered a complication of diabetes and is seen more often in patients whose diabetes is not well controlled. We recommend that all diabetic patients--early or late-onset--have thorough oral examinations and appropriate dental care, along with instructions on maintaining good oral health to avoid complications.

The same need for a clean bill of oral health pertains to cancer patients receiving radiation or chemotherapy. These treatments damage cells that rapidly turn over, such as those lining the mouth or found in the salivary glands. If the patient is already in poor oral health, the cancer treatments can lead to rampant destruction of oral soft and hard tissues, resulting in tooth loss and painful infections of the soft tissues of the mouth. These infections can severely interfere with eating and greatly add to the patient's distress and discomfort.

RESEARCH AND ACTION PROGRAM

Mr. Young. Dr. Löe, you highlight in your statement one of the Institute's programs that is of great concern to me -- The Research and Action Program for Improving the Oral Health of Adults and Older Americans. As the representative of more Americans receiving Social Security benefits than any other member of the House, I am greatly concerned about the frequency of dental examinations and treatment of those living on fixed incomes. After paying the rent, buying food, and providing for their medical care, older Americans often are without funds to have dental checkups. For this reason, our Committee has followed closely your development of this program. Dr. Löe, what progress have you been able to make in the past year on the Research and Action Program for Improving the Oral Health of Adults and Older Americans?

Dr. Löe. In spearheading this initiative, the Institute is playing a dual role: First, in accordance with our mission, we are facilitating the research and science transfer aspects of the Research and Action Program. Second, the Institute is assuming a leadership role in encouraging the participation of other agencies and individuals.

As a result of our efforts, other agencies have become involved through collaborative arrangements, including the Centers for Disease Control, the Indian Health Service, and the Department of Veterans Affairs. Based on actions initiated by NIDR and CDC, the Assistant Secretary has formed an interagency committee to coordinate oral health activities within the Federal government. This committee will have a far-reaching impact on the services and education components of the Research and Action Program that are outside the mission of NIDR.

Staff at NIDR have identified approximately $15 million in ongoing projects that relate to the Research and Action Program and have made recommendations on the facilitation of these and other research efforts. Work continues on several contracts that are investigating the reasons for tooth loss, and high program relevance has been attached to extramural projects including ones investigating improved therapeutics for periodontal diseases and root caries in older adults. The epidemiology of oral diseases and conditions is being investigated in three NIDR-supported research efforts. NIDR has continued active support (with the National Institute on Aging) of a contract with the Institute of Medicine, "Health Promotion in the Second Fifty."

Mr. Young. How was this initiative affected by the budget sequestration imposed by the FY 1990 Budget Reconciliation Bill?

Dr. Löe. The 1.4-percent sequestration was applied to all mechanisms and programs, including the Research and Action Program. Thus, some slowing of this initiative has occurred.

Mr. Young. What are your goals for this program in FY 1990 and FY 1991?

Dr. Löe. The Institute will continue to emphasize the Research and Action Program this year and in the future. Based on an intensive internal review of ongoing extramural and intramural projects, efforts will be made to facilitate those that directly relate to this initiative. Concepts for contracts that relate to the Research and Action Program will be given high program relevance. Several of these concepts are in the process of full development at this time. For example, a request for contract proposals is being developed to investigate the data and research needs to improve the understanding of the oral health of black Americans.

A concept for an interagency effort with the Indian Health Service to study different therapeutic approaches for periodontal diseases is being developed and should be ready for implementation shortly.

Available longitudinal data are being analyzed to determine the nature of risk factors for tooth loss in older adults.

In an effort to encourage more increased extramural focus, an upcoming Program Advisory Committee meeting will focus on the Research and Action Program. Various mechanisms (including Program Announcements, Requests for Proposals, identification of high program relevance, industry collaboration) to encourage extramural funding of research under this initiative are being investigated.

Mr. Young. What level of funding will this program require to meet your FY 1991 program objectives?

Dr. Löe. We estimate that approximately $15 million will be available within the FY 1991 request for steady-state activities associated with the Research and Action Program. Full implementation of the program would require an additional $21 million.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

FY 1991 Budget — Page No.

Appropriation language and explanation of language changes.... 250

Amounts available for obligation............................ 251

Budget mechanism table...................................... 252

Crosswalk tables.. 254

Summary of changes.. 257

Budget authority by activity................................ 259

Budget authority by object.................................. 260

Significant items in Senate and House Appropriations committee reports......................... 262

Authorizing legislation..................................... 264

Appropriations history...................................... 265

Justification:

- A. General statement................................... 267
- B. Program accomplishments............................. 270
- C. AIDS research program............................... 274
- D. Oral diseases and disorders research................ 277
- E. Intramural research................................. 285
- F. Research management and support..................... 292
- G. Detail of permanent positions....................... 293
- H. Advisory and assistance services.................... 295

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

For carrying out section 301 and title IV of the Public Health Service Act with respect to dental diseases, [$138,053,000] $140,520,000.

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1990.)

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Amounts Available for Obligation [1/]

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation	$132,578,000	$138,053,000	$140,520,000
Enacted administrative reduction	-1,826,000	-407,000	---
Sequester order	---	-1,897,000	---
Subtotal, adjusted appropriation	130,752,000	135,749,000	140,520,000
Real transfer to: Health Resources and Services Administration for AZT grants	-43,000	---	---
Comparative transfer to: Division of Research Resources for administrative costs of the RCMI program	-4,000	---	---
Fogarty International Center for passport activities	-5,000	-5,000	---
Comparative transfer from: Office of the Director, NIH, for non-AIDS positions	+326,000	---	---
Subtotal, adjusted budget authority	131,026,000	135,744,000	140,520,000
Unobligated balance, lapsing	-20,000	---	---
Total obligations	131,006,000	135,744,000	140,520,000

1/ Excludes $3,000 for royalties received in 1989, and the following amounts for reimbursable activities carried out by this account: 1989 - $1,516,000; 1990 - $1,634,000; and 1991 - $1,691,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Budget Mechanism
(Dollars in thousands)

	1989 Actual		1990 Appropriation		1991 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects:						
Noncompeting	284	$44,155	284	$46,852	269	$46,453
Administrative supplementals	(2)	76	(3)	152	(3)	160
Competing projects:						
Renewal	47	7,745	39	6,709	43	8,120
New	61	9,761	51	8,463	60	10,243
Supplemental	1	10	0	0	0	0
Subtotal, competing	109	17,516	90	15,172	103	18,363
Subtotal, research projects	393	61,747	374	62,176	372	64,976
Research centers:						
Specialized/comprehensive centers	19	14,478	21	15,936	21	15,936
Other research:						
Research career program	155	8,847	127	9,153	127	9,156
Minority biomedical support		146		161		175
Other research related	58	1,932	57	1,563	57	1,563
Subtotal, other research	213	10,925	184	10,877	184	10,894
Total, research grants	625	87,150	579	88,989	577	91,806

Training:						
Individual awards:						
Noncompeting	19	522	21	618	20	588
Competing:						
Renewal	---	---	---	---	---	---
New	16	429	8	287	9	317
Subtotal, individual	35	951	29	905	29	905
Institutional Awards:						
Noncompeting	132	3,653	135	3,737	156	4,280
Competing:						
Renewal	2	26	21	273	14	182
New	20	674	30	978	16	526
Subtotal, institutional	154	4,353	186	4,988	186	4,988
Total, training	189	5,304	215	5,893	215	5,893
Research and development contracts	19	4,173	20	4,271	20	4,354
	FTEs		FTEs		FTEs	
Intramural research	262	25,870	263	26,995	270	28,567
Research management and support	73	8,529	78	9,303	84	9,900
Extramural Construction		0		293		0
Total	335	131,026	341	135,744	354	140,520
HIV/AIDS	(16)	(4,141)	(18)	(4,662)	(19)	(5,002)

1/ Includes approximately $293,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

CROSSWALK - 1989 Actual
(Dollars in thousands)

	MECHANISM								
	Research Grants			Training Programs					
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional	R & D Contracts	Intramural Research	Research Management & Support	Total
Oral diseases and disorders research..	$61,747	$14,478	$10,925	$951	$4,353	$4,173			$96,627
Intramural research...							$25,870		25,870
Research management and support.........								$8,529	8,529
Total.................	61,747	14,478	10,925	951	4,353	4,173	25,870	8,529	131,026

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

CROSSWALK - 1990 Appropriation 1/
(Dollars in thousands)

	MECHANISM									
	Research Grants			Training						
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional	R & D Contracts	Intramural Research	Research Mgmt. & Support	Construction	Total
Oral diseases and disorders research......	$62,176	$15,936	$10,877	$905	$4,988	$4,271				$99,153
Intramural research							$26,995			26,995
Research management and support....								$9,303		9,303
Extramural construction...									$293	293
Total...........	62,176	15,936	10,877	905	4,988	4,271	26,995	9,303	293	135,744

1/ Includes approximately $293,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

CROSSWALK - 1991 Estimate
(Dollars in thousands)

	MECHANISM								
	Research Grants			Training Programs					
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional	R & D Contracts	Intramural Research	Research Management & Support	Total
Oral diseases and disorders research..	$64,976	$15,936	$10,894	$905	$4,988	$4,354			$102,053
Intramural research...							$28,567		28,567
Research management and support.........								$9,900	9,900
Total................	64,976	15,936	10,894	905	4,988	4,354	28,567	9,900	140,520

National Institute of Dental Research

Summary of Changes

1990 Estimated budget authority..................................	$135,744,000
1991 Estimated budget authority..................................	140,520,000
Net change..	+4,776,000

	1990 Current Estimate Base		Change from Base	
Changes:	Pos. (FTEs)	Budget Authority	Pos. (FTEs)	Budget Authority
A. Built-in:				
1. January 1991 pay raise..........	---	$16,867,000	---	+$586,000
2. Annualization of January 1990 pay raise....................	---	16,867,000	---	+154,000
3. Within-grade increases..........	---	16,867,000	---	+175,000
4. One extra day of pay............	---	16,867,000	---	+67,000
5. Federal Employees Compensation Fund increase....	---	57,000	---	+2,000
6. Unemployment compensation increase......................	---	27,000	---	+1,000
7. Additional FTEs.................	---	16,867,000	---	+630,000
	(341)		(+13)	
8. FTS rate increase...............		246,000		+6,000
9. Payment for centrally furnished services............		7,070,000		+342,000
10. Service and Supply fund increase.................		3,144,000		+20,000
11. Decreased cost of DHHS Working Capital Fund..........		228,000		-10,000
12. Increased cost of laboratory supplies, materials and other expenses................		12,597,000		+415,000
Subtotal...............				+2,388,000
B. Program:	No.	Amount	No.	Amount
1. Research projects:				
a. Noncompeting..............	284	$47,004,000	-15	-$391,000
b. Competing.................	90	15,172,000	+13	+3,191,000
Subtotal, grants.........	374	62,176,000	-2	+2,800,000
2. Other research..................	184	10,877,000	---	+17,000
3. R&D contracts...................	20	4,271,000	---	+83,000
4. Extramural construction.........		293,000		-293,000
5. Intramural research: program decrease.......................		26,995		-81,000
6. Research Management and Support: program decrease..............		9,303		-138,000
Subtotal...............				+2,388,000
Total changes..........				+4,776,000

National Institute of Dental Research

Budget Authority by Activity

	1989 Actual		1990 Appropriation 1/		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Oral diseases and disorders research....		$96,627,000		$99,153,000		$102,053,000
Intramural research.....	262	25,853,000	263	26,995,000	270	28,567,000
Research management and support...............	73	8,526,000	78	9,303,000	84	9,900,000
Extramural construction.		---		293,000		---
Subtotal, obligations.	335	131,006,000	341	135,744,000	354	140,520,000
Unobligated balance, lapsing...............		20,000		---		---
Total budget authority.........	335	131,026,000	341	135,744,000	354	140,520,000
HIV/AIDS	(16)	(4,141,000)	(18)	(4,662,000)	(19)	(5,002,000)

1/ Includes approximately $293,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Total number of full-time permanent positions.................	236	250	+14
Total compensable workyears:			
Full-time equivalent employment........................	345	358	+13
Full-time equivalent of overtime and holiday hours........	3	3	---
Average ES salary.....................	$73,187	$75,750	+$2,563
Average GM/GS grade...................	9.4	9.4	---
Average GM/GS salary..................	$31,882	$33,000	+$1,118
Average salary, grades est. by act of July 1, 1944 (42 USC 207)........	66,016	68,330	+2,314
Average salary of ungraded positions..........................	18,431	19,100	+669
Personnel compensation:			
Full-time permanent................	$8,855,000	$9,692,000	+$837,000
Other than full-time permanent......	4,156,000	4,549,000	+393,000
Other personnel compensation........	454,000	497,000	+43,000
Special personnel services..........	886,000	970,000	+84,000
Total personnel compensation......	14,351,000	15,708,000	+1,357,000
Personnel benefits....................	2,516,000	2,753,000	+237,000
Travel and transportation of persons..	534,000	554,000	+20,000

	1990 Appropriation	1991 Estimate	Increase or Decrease
Transportation of things..............	$82,000	$85,000	+$3,000
Rent, communicatons and utilities.......................	744,000	772,000	+28,000
Printing and reproduction.........	160,000	166,000	+6,000
Other services:			
Project contracts............	4,271,000	4,354,000	+83,000
Centrally furnished services...................	6,401,000	7,012,000	+611,000
Standard level user charge...	669,000	400,000	-269,000
Other........................	5,915,000	5,615,000	-300,000
Supplies and materials............	3,965,000	4,104,000	+139,000
Equipment.........................	1,254,000	1,298,000	+44,000
Grants, subsidies & contributions..................	94,882,000	97,699,000	+2,817,000
Total, budget authority......	135,744,000	140,520,000	+4,776,000

National Institute of Dental Research

Significant Items in House Appropriations Committee Report

Item	Action Taken or to Be Taken
Research Centers "...the Institute should give consideration to the need for dental research centers." (Page 57)	The NIDR issued a Request for Applications for the establishment of dental clinical core research centers in October 1989. Receipt date for applications is March 1990. Depending on the outcome of peer review, the Institute hopes to award two new center grants.
TMJ Disorders "...particular interest is research involving temporomandibular joint (TMJ) disorders. Findings to date indicate that 1 in 10 Americans may be troubled by persistent TMJ-associated discomfort. The Institute plans to encourage additional research in this area in FY 1990. The Committee would encourage the Institute to establish a center focusing on this problem if scientifically justified." (Page 58)	To encourage much-needed basic and clinical research on this topic, the NIDR is issuing several solicitations for grant applications.

National Institute of Dental Research

Significant Items in Senate Appropriations Committee Report

Item	Action Taken or to Be Taken
TMD-Related Disorders "The NIDR has indicated that further study is needed to determine how widespread the disorder is and whether various dental practices may promote development of TMD. The Committee encourages the NIDR to pursue research to improve the understanding of TMD-related disorders and to identify effective diagnostic and treatment procedures for this condition." (Page 119)	To encourage much-needed basic and clinical research on TMD-related disorders, the NIDR is issuing several solicitations for grant applications.
Nursing "The Committee strongly urges NIDR to utilize nursing knowledge and expertise by systematically ensuring that professional nurses are involved in its programs and activities." (Page 120)	The NIDR has begun discussions with the National Center for Nursing Research on the development of possible collaborative efforts in areas of mutual interest such as pain research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Authorizing Legislation

Request	PHS Act/ Other Citation	U.S. Code Citation	1990 Amount Authorized	1990 Estimate	1991 Amount Authorized	1991 Budget Request
Research and Investigation.......	Section 301	42§241	Indefinite	$129,851,000	Indefinite	$134,627,000
National Institute of Dental Research....	Title IV, Part Section 453	42§285h 288c	Indefinite		Indefinite	
National Research Service Awards.....	Section 487	42§288	Such sums 1/ as necessary	5,893,000	Authorizing legislation to be requested	5,893,000
Total Budget Authority..				135,744,000		140,520,000

1/ This training authority is shared with the research training program of the Alcohol, Drug Abuse and Mental Health Administration.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriaton 1/
1982	$65,672,000 2/	$75,277,000	$76,557,000	$71,983,000
1983	74,462,000	80,304,000	77,416,000	79,292,000
1984	80,679,000	84,226,000 3/	84,398,000 3/	88,674,000
1985	91,096,000	98,451,000 4/	95,826,000	100,688,000
1986	98,841,000	97,691,000 5/	103,728,000	103,282,000
1986 Sequester				-4,441,000
1987 6/	96,482,000	116,275,000	116,553,000	117,945,000
1988	113,602,000	129,106,000 7/	131,559,000	126,297,000
1989	127,157,000 8/	127,315,000 9/	132,578,000	130,752,000
1990	131,527,000 10/	138,053,000	137,096,000	137,646,000
1990 Sequester				-1,897,000
1991	140,520,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Reflects the September amendment; the original request was $74,627,000.

3/ Excludes $3,735,000 in NRSA training programs not considered.

4/ Excludes $4,687,000 in NRSA training programs not considered.

5/ Excludes $4,562,000 in NRSA training programs not considered

6/ The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House allowance consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate allowance and the appropriation spread the funding among the Institutes, including $2,733,000 for the National Institute of Dental Research.

7/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

8/ The request excludes funds for AIDS research and education ($3,562,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

9/ Excludes $5,368,000 in NRSA training programs not considered.

10/ The request excludes funds for the National HIV Program ($4,269,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

Justification

National Institute on Dental Research

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Total....	341	$135,744,000	354	$140,520,000	+13	$4,776,000
HIV/AIDS	(18)	(4,141,000)	(19)	(5,002,000)	(+1)	(+340,000)

General Statement

The National Institute of Dental Research (NIDR) conducts and supports research and research training on oral diseases and disorders. Research on the major dental diseases--dental caries and periodontal diseases--has led to new understanding of how to prevent or control these diseases, so that it is entirely possible that future generations need not lose a single tooth to disease but, instead, preserve the natural dentition throughout their lifetime. This important goal is being pursued in research that explores all aspects of oral tissue growth, development, aging, maintenance, and repair--taking into consideration the dynamics of the oral environment as well as genetic, immunological, microbiological, hormonal, neural, nutritional, and behavioral variables that affect oral structures and functions.

Research is conducted on craniofacial developmental abnormalities such as cleft palate, on genetic diseases affecting teeth and bones, on facial trauma and wound healing, on the salivary glands and on sensorimotor functions such as taste, chewing, swallowing, and the perception and control of pain, wherever it occurs in the body.

Specific diseases and disorders of oral tissues important in oral health research include herpesvirus infections, aphthous ulcers (canker sores), autoimmune disorders such as Sjogren's syndrome, salivary gland dysfunctions, oral cancers, and AIDS.

NIDR supports extramural research and research training through three program areas: dental caries and restorative materials; periodontal diseases, mineralized and soft tissue diseases (including AIDS), nutritional research, and dental implants; and craniofacial anomalies, pain, and behavioral science research. Intramural research is conducted at nine laboratories and at a dental clinic and pain research unit located in the NIH Clinical Center.

The Institute has completed a draft of its Long-Range Research Plan for the Nineties. The Plan describes achievements during the eighties and poses research recommendations for the nineties across a broad range of research areas--"from AIDS to xerostomia." In a departure from earlier plans, this one establishes research priorities. These include studies of medical problems that directly affect oral health (including common diseases such as diabetes and "orphan" diseases such as ectodermal dysplasia); studies of oral health problems that merit increased attention, such as oral cancers, certain pain problems, and disorders of taste and smell; implementation of the research-related portion of the Research and Action Program for Improving the Oral Health of Adults and Older Americans (described below); and efforts to finish the job of eliminating dental caries and the periodontal diseases as major health problems. At the same time, broad-ranging basic research, particularly using the techniques of cell and molecular biology, will be encouraged to allow investigators to pursue ideas that may very well signal the next revolution in biomedical research. To facilitate these activities, Institute plans are calling for new and expanded collaborations with health professional and voluntary organizations and other consumer groups, government and private research organizations (both domestic and international), and the private sector. Special efforts will be undertaken to improve the oral health of ethnic and racial minority groups and to recruit minorities to careers in oral health research.

We have made the Research and Action Program one of our high priorities for the coming decade. The program has developed in response to findings from a recent NIDR survey that showed significant levels of oral health problems as well as toothlessness among the nation's older citizens. The Institute will pursue basic and clinical research on normal age-related changes in the oral tissues as well as changes due to oral or systemic disease and treatments. "Action research" will involve NIDR in the transfer of laboratory findings to public and professional use through clinical trials, demonstration research, and similar efforts. The goals of the program are to eliminate toothlessness in the United States within the next 20 years and to prevent further deterioration in the oral health of individuals with already compromised dentitions. We are placing special emphasis on identifying individuals, of any age, who are at risk for oral health problems for whatever reason (dental, medical, socioeconomic, etc.). In the past year, we have worked closely with the Centers for Disease Control, which will assume responsibility for working with state and local health agencies in implementing oral health promotion and disease prevention activities at state and local levels. In addition, we have gained the enthusiastic support for the program by other government agencies, including the Indian Health Service and the Health Resources and Services Administration.

Overall Budget Policy

The 1991 budget request for NIDR favors basic research and totals $140,520,000, an increase of $4,776,000 over the comparable 1990 level of $135,744,000. Included in the request is provision for AIDS research at $5,002,000, an increase of $340,000 over the 1990 amount.

At the 1991 request level, the Institute will support 269 noncompeting research project grants at $46,613,000 and 103 competing grants at $18,363,000, compared to 284 and 90, respectively, in 1990.

Research centers will remain at the 1990 level: 21 centers at $15,936,000.

The other research grant category includes an increase of $17,000, which is primarily for minority biomedical research support.

Approximately 215 full-time training positions at a cost of $5,893,000 will be supported within the 1991 request for research training--the same as the 1990 level.

A total of $4,354,000 will be available for R&D contracts, compared to $4,271,000 in 1990.

Support for the intramural research program will be at $28,567,000 and 270 FTEs, compared to $26,995,000 and 263 FTEs in 1990.

Research management and support activities will be funded at $9,900,000 and will include 84 FTEs. The 1990 amounts were $9,303,000 and 78 FTEs.

Program Accomplishments

Although the incidence of dental caries has been markedly reduced in children, it remains highly prevalent in adults and, together with periodontal disease, is a major factor in the loss of teeth in older Americans. We have found that long-term residents in areas with nonfluoridated water, when compared to those in fluoridated communities, have a greater risk of dental disease. In other studies, we discovered that older Americans who use fluoride rinses have fewer caries affecting the roots of teeth.

Epidemiologists have discovered certain unexplained racial differences in the oral health of the elderly. For example, the mean number of teeth among black persons 65 years old and older is less than for whites; in fact, blacks are more likely to have fewer than 12 teeth. Because older whites have a lower rate of tooth loss, they have three times as many cavities as blacks. We have also found that older whites have significantly more root caries than older blacks, but black seniors currently need significantly more root caries treatment. These differences prevail even when controlled for education, socioeconomic status, and residence.

Our investigators have developed safe, short-term, intraoral methods that reduce dramatically the need for animals in caries research. Appliances containing samples of tooth surfaces placed in the mouth show that the production of acids that can dissolve tooth enamel by caries-promoting foods can be decreased by supplementing the diet with foods known to stimulate saliva flow and/or prevent acid accumulation in dental plaque. We have also used these methods to test various fluoride regimens for their effectiveness in preventing caries or restoring tooth enamel after acid attack. These studies should lead to the "ideal" mouthrinse to prevent dental caries in high-risk populations.

A few months ago, the Institute awarded grants for three Specialized Materials Science Research Centers to develop new or improved restorative and maxillofacial materials. The new centers will be funded for 5 years and are located at the University of Michigan, the University of Florida, and the Paffenbarger Research Center of the American Dental Association. The need for these Materials Centers was highlighted as a result of the 1986 national survey of employed adults and older Americans. This survey revealed that 42 percent of those aged 65 and older, and 4 percent of employed adults, are missing all their teeth; one-half of employed adults have lost at least one tooth; and 63 percent of seniors and 21 percent of employed adults have root caries. All these problems require restorative materials.

Our researchers have devised a new treatment for localized juvenile periodontitis--a relatively rare but severe form of periodontal disease that affects the front and molar teeth of teenagers and young adults. Familial and genetic factors seem to be important in the disorder; microbiology studies also indicate that a particular bacterial species is involved. When conventional therapeutic procedures are successful in eliminating the organism, the disease does not progress. However, in a quarter of the cases, these measures fail and the disorder progresses to a severe form, with eventual loss of teeth. We tested a combination of two antibiotics, metronidazole and amoxicillin, which improved the patients' condition immediately and eliminated the causative organism.

Metronidazole alone has also been shown to be effective in treating chronic periodontitis in adults, the most common form of periodontal disease. We designed clinical trials to test whether an optimized schedule of metronidazole, coupled with conservative dental care to reduce plaque build-up, could reduce the need for periodontal surgery. Neither the patients nor the examiners knew which patients were receiving the actual medication and which were receiving the placebo. One week of metronidazole followed by conservative dental care reduced the need for surgery by an average of five teeth per patient, compared to the controls, who received placebo drug plus conservative care. This difference was maintained throughout the 2- to 3-year recall period.

We have witnessed impressive advances in understanding the optimal conditions for transplantation and regeneration of skeletal muscles in the treatment of facial injuries and paralysis. For example, rat muscles, deprived of nerve endings for as long as 22 months, are spontaneously reinnervated when they are transplanted into innervated limbs. However, old hosts do not provide as optimal an environment as young ones for muscle regeneration following transplantation. Immediate repair of the blood vessel connections is essential to prevent degeneration of muscle fibers following transplantation, but, even with immediate revascularization, functional deficits remain. These deficits are a serious limitation to more widespread use of skeletal muscle transplantation in treating facial injuries. We note, however, that post-operative rehabilitation procedures increase the responses of grafted muscles, both in numbers and intensity.

Our investigators have made major strides in understanding how to increase patient compliance with dental preventive and treatment programs. Behavioral scientists working with orthodontists have developed a series of behavioral interventions--acceptable to both young adolescent patients and their families, and practical to implement in regular dental offices--which yield patient behaviors that markedly increase rates of successful orthodontic treatment. Similarly, studies with adult periodontal patients have shown more efficient, prolonged plaque removal behaviors in those who participate in a motivational/educational program, which involves repeated microscope viewing of disease bacteria sampled from their own mouths.

Nerve injury can result in a type of chronic pain for which opiate analgesics provide no relief. When peripheral nerves are injured, a complex sequence of changes occurs in the function of central nervous system structures to which the injured peripheral neurons normally project. Our neuroscientists have delineated changes occurring in higher order nerve cells in the brain following injury to nerves in the face and teeth. These include increased excitability and changes in size of the area in skin or tooth pulp to which they respond. Persistence of these neuronal changes is now thought to underlie the often severe pain that can follow nerve injury.

Studies by NIDR investigators in collaboration with scientists from the National Institute on Aging are debunking a common generalization about aging and oral health--that food enjoyment, especially the sense of taste, is diminished in aging. We have shown that healthy men and women, regardless of their age, are quite similar in their ability to discern the four basic taste modalities (sweet, sour, salty, and bitter). We have also observed that older persons are as competent as younger persons in judging the texture and the temperatures of various foods. However, persons over 65 do show impairments in the sense of smell. These studies suggest that, in healthy older persons, complaints of decreased food enjoyment likely reflect a diminished olfactory sense.

In other studies, we have examined salivary gland function in patients with early-stage Alzheimer's disease. These individuals were generally in good physical health, neither taking any prescription medications nor being treated for any other medical condition. NIDR scientists had previously shown that, in healthy persons, salivary gland function remains intact with age. In our most recent studies, we have shown that the Alzheimer's patients exhibit a selective and marked reduction in the ability to produce submandibular and sublingual gland saliva, while maintaining normal levels of parotid gland saliva. These results suggest that this unique type of salivary dysfunction could represent a specific defect in seventh cranial nerve activity.

For some time we have suspected that intrinsic differences in saliva can explain, in part, why some people are resistant and others susceptible to dental caries. Our studies now suggest that it is the composition of the fatty components of saliva--the lipids--that makes the difference. Saliva from caries-resistant individuals retards the diffusion of acids onto tooth enamel. When the lipid component is removed, however, acid diffusion increases. We suspect that compositional differences in the lipids from the salivas of caries-resistant and caries-susceptible individuals may explain the differences in acid-retarding ability.

Saliva contains high concentrations of calcium phosphates used to repair dental enamel. Several proteins in saliva maintain these compounds in solution by actively inhibiting the formation of calcium phosphate crystals. We have now determined the amino acid sequences of several of these proteins and consequently have a better understanding of their mode of action. This information will be important in developing artificial salivas needed by millions of Americans who suffer primary or secondary salivary gland dysfunctions.

A clinical study of dental implants in patients missing all their teeth and in children with ectodermal dysplasia (a genetic disease that affects skin and teeth) has enrolled 75 patients. The titanium implants have successfully integrated with bone and soft tissue in both types of patients. We are evaluating the effect of the implants on patient satisfaction with treatment, body image, ability to chew various types of food, and maintenance of supporting bone. The psychological aspects of satisfaction with treatment are also being evaluated. We have found that complications due to bio-mechanical factors occur, and that some patients are not satisfied with standard implant treatment procedures; however, the majority of patients are very satisfied with the treatment and report an increased ability to chew food and a greater sense of security when speaking. We plan to increase the study population to about 130 patients and to follow them for 5 years.

Two major national initiatives in data collection have begun: (1) a comprehensive oral examination component in the 1988-1994 National Health and Nutrition Examination Survey (NHANES III), and (2) a 1989 National Health Interview Survey supplement on oral health, including several questions on symptoms of oral-facial pain. Furthermore, we are collaborating with the Department of Veterans Affairs in a longitudinal dental study designed to provide information on the use of, and actual charges for, dental services over the past decade.

AIDS Research Program

NIDR AIDS Program

The NIDR AIDS program supports and conducts research on the oral manifestations associated with HIV infection and the role of saliva in the transmission or inhibition of HIV and other pathogenic organisms. These objectives are pursued primarily though research grants, R&D contracts, and the intramural research program.

Recent Research Accomplishments

The key to effective intervention in AIDS is early and accurate detection of the virus. In a sample of men at high risk for AIDS, NIDR-supported investigators, using a DNA probe, were able to detect HIV in the fluid from crevices in the gums as frequently as the traditional Western Blot test could detect HIV antibody in the serum. Moreover, of those subjects who were seronegative by the Western Blot test, four showed HIV in the gum fluid; one of these subjects became seropositive as judged by the Western Blot method 2 months later. These findings show that HIV infection can be detected in the mouth well before a serum antibody response develops. This technique may provide a more accurate, less invasive, and earlier diagnosis than currently available.

Candidiasis, the most prevalent oral lesion in AIDS, is caused by a fungus. If unchecked, the infection can spread to the intestinal tract, increasing disease morbidity. Recent studies in the NIDR intramural program involving this fungus indicate that the presence of this and other opportunistic infections is not due to unique or particularly virulent strains of microorganisms but is the result of defective host mechanisms. Renewed efforts have focused on abnormal immune function in the patients. In this regard, blood monocytes, one of the most important cells to fight off bacteria and fungi, have been studied in AIDS patients and found to exhibit unique functional and phenotypic properties. Dipyridamole (DPM) has been shown to enhance the inhibitory effects of AZT and [2',3']-dideoxycytidine against HIV in human monocytes. Since monocyte lineage cells appear to be a major reservoir for HIV in vivo, these findings suggest the possibility of using DPM or its analogues in combination chemotherapy of HIV infections.

"Hairy leukoplakia" is a whitish lesion that generally occurs on the surface of the tongue. Several laboratories have confirmed that it is the second most prevalent oral manifestation of HIV infection, and is considered predictive of frank AIDS. Although other microorganisms are found in this unique lesion, Epstein-Barr virus is believed to be the primary pathogen, because it is often present in overwhelming numbers. Because the lesion is so reliable as a predictor of the subsequent development of AIDS, NIDR is vigorously pursuing studies of its causes, early diagnosis, and means of prevention and treatment.

NIDR intramural researchers have continued to explore the effects of HIV infection on human salivary gland secretions. Saliva is a key component of oral defense, containing antibodies as well as antimicrobial factors. Early in the course of HIV infection, human submandibular gland secretions show significant alterations in levels of protective proteins. In a recent longitudinal study of HIV-infected individuals, NIDR scientists showed that submandibular compositional changes persisted and that similar changes began to appear in the parotid gland secretions. Thus all major salivary glands become involved following HIV infection. The salivary alterations found may play a role in the high prevalence of oral lesions associated with HIV infection.

An important issue to be resolved is the role of saliva and the oral cavity in transmission of HIV. HIV can be recovered from the oral cavity and has been found in parotid saliva. However, the mouth and saliva do not appear to be routes of viral transmission. NIDR intramural scientists have shown that human saliva, in particular submandibular secretions, can inhibit the ability of HIV to infect lymphocytes. Inhibitory activity was found in all individuals studied, including healthy men, women, and children and HIV-infected men. To verify these provocative findings and to characterize and study the mechanisms of action of such putative factors, the NIDR issued a Request for Applications in FY 1989. Fourteen applications are under expedited review. Several of the most meritorious applications are expected to be funded in FY 1990.

In 1988, NIDR, in collaboration with NIAID, created a small transgenic animal model containing intact copies of HIV. NIDR has continued to use the transgenic mouse technology in dissecting the pathogenesis of HIV using individual HIV genes. Mice have been created that bear all or some of the HIV genes stably incorporated in their genomes; several manifest AIDS-related pathologies. As a result, models are becoming available for studying juvenile AIDS, fetal abortion, and HIV-associated kidney disease. These animals will be a valuable resource for improving our understanding of disease progression in AIDS patients and for the direct testing of protocols for disease intervention.

A new research project has been initiated to investigate the feasibility of developing a sustained-release bioadhesive delivery system for an anti-fungal drug that would be suitable for the prevention and/or treatment of oral candidiasis. It is anticipated that, at the completion of this project, sufficient data will have been collected from both laboratory and animal studies to determine if human testing of the delivery systems developed under this project is warranted.

The NIDR oral health research facility located in a newly renovated ward at the U.S. Walter Reed Army Medical Center was officially opened on May 30, 1989. The facility will be used for the study of oral manifestations of HIV infection, and is part of a broader natural history study conducted by the Walter Reed Army Institute of Research. The objective is the documentation of the prevalence and incidence of oral diseases and conditions and their relation to the progression of HIV infection as well as to systemic diseases. Specific areas of investigation include oral candidiasis, periodontal diseases, microbiology, and compositional changes in saliva. To date, approximately 100 subjects have been examined. It is anticipated that about 1,000 individuals will be reexamined every 6 months during the course of their disease.

Research Plans

The NIDR will continue to support and conduct research on the oral manifestations associated with HIV infection and on the role of saliva in the transmission or inhibition of HIV and other pathogenic organisms. Research grants will range from basic laboratory studies on the molecular biology of the opportunistic fungus *Candida albicans* to epidemiologic studies of large cohorts of individuals at risk for HIV, who are being examined for opportunistic oral lesions and tested to determine sero-status.

Since the role of saliva in HIV infection has not been fully clarified, studies will be devoted to the role of saliva in transmission and will investigate the potential antiviral, non-immune properties of saliva against herpes simplex virus, Epstein-Barr virus, and cytomegalovirus--all of which have been detected in oral lesions of AIDS patients.

The concentrations of relevant salivary constituents will be determined in the salivas of normal controls and immunologically compromised AIDS patients. The data obtained could contribute to the understanding of the *in vivo* pathogenesis of recurrent herpesvirus infections in patients without AIDS and provide new insight into the non-immune protective mechanisms of saliva in individuals with other types of severe immunodeficiencies.

The collaborative project with Walter Reed will continue. This study is documenting AIDS-related oral changes with disease progression, changes in oral ecology, and effective treatment of oral conditions.

National Institute of Dental Research

Oral Diseases and Disorders Research

Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$99,153,000	$102,053,000	+$2,900,000

Purpose and Method of Operation

The purposes of research activities in this area are to increase knowledge on the causes, development, treatment, and prevention of dental caries and periodontal diseases so that our natural teeth can be maintained throughout life; to develop improved restorative materials and devices for the prevention and treatment of oral diseases; to improve knowledge of the development, structure, function, and diseases of the salivary glands and to determine the influence of salivary constituents on oral health; to develop knowledge of relationships between nutritional factors and oral health or disease; to investigate the causes and methods of preventing and treating oral soft tissue diseases such as canker sores, herpes infections (fever blisters or cold sores), oral manifestations of AIDS, and oral cancer. Additionally, NIDR research activities are designed to increase understanding of the cause, prevention, and treatment of congenital anomalies such as cleft lip and palate, of malocclusion of the teeth and jaws, and of the disfigurements that occur through accidents or surgical procedures; to expand our knowledge of the causes of acute and chronic orofacial pain, and to develop improved methods for preventing, diagnosing, and treating such conditions; and to determine the impact of behaviors on risks for oral disease and to identify behavioral approaches for improving prevention, diagnosis, or treatment of oral diseases. These objectives are pursued through the use of research project grants, research centers, other research grants, R&D contracts, and research training.

Rationale for the Budget Request

The 1991 request of $102,053,000 for this activity represents an increase of $2,900,000 above the 1990 level. Program plans, along with expected accomplishments, are as follows:

Dental Caries

Americans can be understandably encouraged by the recent finding that dental caries in children ages 5 to 17 is continuing to decline. A nationwide survey conducted by NIDR in 1986-87 showed that the average school child had about 33 percent fewer decayed, missing, or filled permanent tooth surfaces than in 1980; furthermore, half the children had never had cavities in their permanent teeth. This decline in dental caries amounts to an estimated savings of about $3 billion a year in the nation's dental bill. Unfortunately, substantial levels of caries remain in older children and in particular subgroups of the U.S. population, and are actually increasing in some developing countries.

In studies of the transmission of dental diseases, we have learned that infants do not acquire the caries-causing bacteria that colonize the mouth and digestive tract until after birth, usually in the course of normal handling by the mother and other family members. We now know that it is possible to "interfere" with mother-offspring transmission of cariogenic bacteria by treating mothers with antibiotics or antimicrobial mouth rinses such as chlorhexidine, which is available as a prescription drug. This mouth rinse is also effective in lowering the risk of caries in children already found to harbor high levels of cariogenic bacteria in the mouth.

Researchers conducting molecular biology studies of cariogenic bacteria have established that certain bacterial proteins play a key role in the disease process. These investigators have recently found that mutant forms of bacteria, which lack these "virulence" factors, do not infect experimental animals, even when the animals are fed diets rich in sugar. They are pursuing the possibility of developing safe forms of bacteria that could be implanted in the mouth to replace disease-causing bacteria.

In other immunologic studies, investigators have shown that direct application in the oral cavity of monoclonal antibodies against the principal caries-causing bacteria is effective in protecting against disease. Passive immunity--achieved, for example, by drinking milk from cows immunized against caries by injection with caries-causing bacteria--can delay colonization of caries bacteria in children and result in a reduced incidence of caries.

A major focus of basic research on oral diseases is on how and where bacteria become established in the mouth and how the various species interact with each other and with oral tissues. This "oral ecology" approach has led to the discovery of various "adhesion" molecules on the surface of bacteria that can bind to receptors on oral tissues, on other bacteria, or on the thin membranous covering of the teeth called the pellicle. Some caries-causing bacteria are also able to extrude molecules that can stick to the tooth surface. These molecules can, in turn, act as points of attachment for other bacteria. Thus, one species of bacteria can facilitate the colonization of other species.

Restorative Materials

We have seen marked improvements in the last few years in the plastic materials used in dental restorations. The tooth-colored substances now available for use on the front teeth provide good performance and are esthetically superior to formerly used materials. Current research is aimed at resolving problems associated with their use on the back teeth, where these materials are subject to greater wear. In FY 1991, we will begin controlled clinical studies using defined criteria to analyze mechanisms covering the behavior of these materials.

Biocompatibility of restorative materials is an important consideration in their development and future use. Consequently, we are supporting several studies that are leading to new criteria and techniques for the laboratory testing of the possible toxicity of restorative materials and other therapies. These studies are expected to result in improved knowledge of the biologic response of dental materials and medicaments when they come in contact with living tissue. We will also pursue research leading to the development of controls to prevent infection and cross-infection of dental personnel and patients in the use of materials, instruments, and equipment.

Salivary Glands and Secretions

Every function of the oral cavity depends on the presence of saliva. It is the lubricant that facilitates speech, taste, chewing, and swallowing. Significantly, saliva also contains components that protect against infections and help maintain and repair the oral tissues.

Salivary gland dysfunction leading to a condition called dry mouth (xerostomia) is a common problem associated with several diseases and disorders. For example, it is estimated that as many as 2 million Americans suffer from Sjogren's syndrome, an autoimmune disease with symptoms of dry eyes and dry mouth. In addition, about 400,000 persons in this country are affected with dry mouth each year as a consequence of head and neck radiation and other cancer treatments. Finally, more than 400 medications in common use can also cause dry mouth. Dry mouth leads to painful sores in the mouth, fungal infections, and rampant tooth decay. In the worst cases, victims can hardly swallow, talk, or eat solid foods. Without saliva, it is possible for a person to lose all the teeth in 6 months.

The clinical treatment of dry mouth is frustrating for the dentist and not always very effective for the patient. The common therapies involve the use of secretory stimulators and artificial salivas, but they do not always relieve the discomfort and pain nor provide needed protection against infection. An ideal artificial saliva should be longlasting, provide lubrication, inhibit colonization by disease bacteria, and coat the oral soft tissues for protection against environmental insult and dryness. Our researchers are conducting studies to determine the structural requirements of salivary molecules responsible for these protective functions. Composite salivary substances can then be developed, which will have multiple functions attributable to different parts of the molecule. These composite molecules can then be targeted to suit an individual patient's particular needs.

Basic research on the salivary glands is benefiting from developments in cell biology that permit development of cultures of salivary gland cells. Techniques are available for transforming and immortalizing cells so that they can be kept indefinitely in culture, while retaining many of their biological characteristics.

Periodontal and Soft Tissue Diseases

Periodontal disease is accompanied by an inflammatory response characterized by swelling, pain, and redness of the tissue. These processes, normally involved in degrading damaged tissues and encouraging healing, are detrimental when they persist, as in the case of periodontal disease. Research interest is focused on the host enzymes that degrade tissue, such as collagenase, which attacks the principal connective tissue component, collagen. The enzyme is released in an inactive form, and it is not known how the molecule is subsequently activated. A search is under way to find agents, in addition to antibodies, to block collagenase action so that tissues may be protected from its deleterious action. Investigators are using crystallography to determine the structure of the enzyme so that drugs can be tailored to fit the active site of the enzyme and prevent its action.

Classical approaches to treatment of periodontal disease are directed at eliminating bacterial plaque in order to halt progressive loss of the connective tissue attachment of the tooth to its supporting structures. A new surgical approach is aimed not just at arresting the disease process, but regenerating the lost tissue. The technique permits only selected cells access to exposed root surfaces. Evidence is accumulating that these cells have the potential to develop into bone and connective tissue cells and also stimulate the formation of cementum, the hard tissue that covers the roots of teeth.

Clinical and animal studies indicate that the critical event in periodontal tissue regeneration is the deposition of cementum. We have now identified a protein that serves as a marker of this cementum deposition, and have produced antibodies to aid in the isolation and purification of the protein. Future studies will focus on genetic control of production and mechanism of action of this factor, which appears to be especially important to the wound healing and tissue regeneration of periodontal tissues.

Maintaining the periodontal health of handicapped individuals, such as mentally retarded patients, is difficult, because they are often unable to perform the usual oral hygiene procedures such as brushing and flossing. In a recent pilot study, our investigators showed the effectiveness of an antibacterial mouth rinse containing chlorhexidine, when applied twice daily for 8 weeks as a spray, to institutionalized, mentally retarded adults with gingivitis. Patients receiving the chlorhexidine spray showed healthier gingival tissues, dramatically decreased plaque, and reduced bleeding. Patients with similar degrees of gingivitis, who brushed their teeth and received a placebo spray, showed no improvement over the 8-week period. This pilot test needs to be duplicated and extended to other high risk groups.

A large ongoing study of urban and rural blacks and whites has shown much higher levels of severe periodontal disease in elderly blacks than in whites, even when statistical adjustments were made to account for differences in health care utilization, education, and income. Blacks were five times more likely than whites to show significant overall loss of attachment between the teeth and the supporting periodontal tissues. Blacks were also much more likely to be infected with a particular periodontal disease bacterial species. Effective interventions to reduce these alarmingly high levels of infection and periodontal disease found in black seniors will require additional understanding of the biological and/or behavioral factors underlying these major differences.

An NIDR collaborative project with the National Institute of Diabetes and Digestive and Kidney Diseases and the Phoenix Area Indian Health Service Program is defining the oral complications of adult onset (Type II) diabetes in Pima Indians, a group with the highest known prevalence of adult diabetes in the world. Nearly 3,000 subjects have been studied over the past 5 years. Overall, diabetic patients are 15 times more likely to be missing all their teeth than are normal subjects. In the Pima Indian group, when diabetes was present for 10 years, 14 percent of patients had lost all their teeth; after 20 years, 75 percent were toothless. The major reason for tooth loss was periodontal disease and its complications. Diabetic patients with retinopathy, a common complication that can lead to blindness, were five times more likely to have periodontal disease than patients without retinopathy. However, no relationship was found between periodontal disease and kidney disease, another frequent complication of diabetes. We found that the degree to which blood glucose was controlled was an important predictor of the presence of periodontal disease. Patients with high blood glucose were twice as likely to have periodontal disease than those whose glucose levels were well controlled. In the next phase of the study, the specific microorganisms associated with this type of periodontal disease and the patients' immune response will be characterized, and treatment will be designed for this high risk, minority population.

Squamous cell carcinomas are cancers of specialized cells found in skin and the mucous membranes that line the mouth, the esophagus, and the respiratory and genital tracts. Human papilloma virus (HPV) is associated with squamous cell carcinoma of the cervix. Our investigators have used very sensitive assays, which identify individual strands of viral DNA in a cell by matching them with known genetic material, to locate HPV in 60 to 90 percent of oral cancers. The malignancies were from the tongue, mouth floor, pharynx, esophagus, sinus, and larynx of patients with a history of tobacco use. Future studies will determine how HPV influences oral cancer and how it relates to other risk factors for oral cancer such as alcohol.

Herpes simplex virus (HSV) infection remains a major public health problem, causing cold sores, eye and genital infections, and encephalitis.

Much research centers on one of the molecules on the surface of the virus, HSV "glycoprotein D," which is essential for viral penetration of the host cell and subsequent fusion within the host DNA. This protein stimulates a variety of host immune responses and is a candidate for a herpes vaccine. In studies to date, animals immunized with glycoprotein D have been protected from subsequent challenges with lethal doses of either HSV 1 (associated with oral herpes infections) or HSV 2 (associated with genital infection). Scientists have cloned the gene for glycoprotein D, and are using sophisticated recombinant DNA techniques to analyze the role of portions of the gene and its protein product. By preparing mutant genes and inserting them into mammalian cells, investigators can determine how the gene changes affect properties of the surface. For example, certain mutations make the virus temperature sensitive. Experiments are under way to determine which portions of the molecule are critical to its activity as a vaccine.

Craniofacial Anomalies

Proper development of the head, face, and mouth requires that the fetal growth and assembly of the component tissues be integrated and coordinated. If they are not, debilitating birth defects result. These processes begin very early in embryogenesis, when precursor cells migrate from their place of origin to their ultimate locations in the head. Interactions between these cells and neighboring tissues are critical in determining routes of migration and differentiation into nerves, muscle, bone, and teeth. Investigators are tracking these events by transplanting cells from one species of bird embryo to another and following their movement as the embryo develops. They have found that muscle precursor cells from any part of the body are able to form normal craniofacial muscles if they are transplanted at an early age. Similarly, blood vessel precursor cells from any part of the embryo can migrate rapidly over great distances and form normal craniofacial blood vessels. In one case, the molecular mechanism enabling cells to migrate has been shown to involve a particular enzyme on the surface of the cell. We will continue our support of these and additional studies aimed at preventing birth defects of the head, face and mouth.

Many children and an increasing number of adults in the United States are receiving treatment for correction of malocclusions. Because of the frequent discomfort and high cost associated with these procedures, the Institute is conducting clinical trials to compare the efficacy of alternative treatments. A common form of malocclusion is characterized by protrusion of the upper front teeth, most frequently caused by underdevelopment of the lower jaw. Three common treatments are being compared: orthopedic modification of jaw growth prior to adolescence, followed by movement of teeth during adolescence; combined repositioning of the teeth and compensation of jaw discrepancies during adolescence, when permanent teeth have erupted; or surgical-orthodontic repositioning of the jaws and teeth during late adolescence or in young adults. Results of these studies will be available in about 4 years.

Several groups of scientists are investigating how tooth enamel develops and becomes mineralized, forming the hardest tissue in the body.

Two classes of proteins with different amino acid compositions, known as enamelins and amelogenins, are secreted by enamel-forming cells. Investigators are cloning the genes for some of these proteins in order to determine how they are produced and precisely what part they play in enamel formation. Some studies indicate that different types of amelogenins occur because of different RNA splicing mechanisms, rather than because they are the products of different genes. Other groups of researchers are working on the theory that various amelogenins arise by degradation of parent proteins. The degree of crystallization of enamel increases as it matures. Fluoride is preferentially taken up by developing enamel and incorporated into the developing enamel crystal. The distribution of fluoride observed in mature teeth, with high concentrations at the surface and lower concentrations toward the dentin within the tooth, is already apparent in teeth at the time of birth. This emphasizes the importance of supplying fluoride around the time of birth and prior to tooth eruption in order to confer its protective effect and prevent future caries.

Pain Control and Behavioral Research

The experience of pain is a subjective event that, unfortunately, cannot be observed directly. To evaluate whether pain is actually present, and whether it is changing in response to disease progression or to treatment, scientists rely on subjective reports by the patient, observations of restrictions in movements, and other indirect measures. Better indicators of pain experience, not under the direct control of the patient, can provide important scientific and practical benefits.

Dental researchers have found that facial muscle movements and expressions, which can be rated very reliably, provide sensitive indicators of pain occurring with tooth abscesses and chronic orofacial pain conditions such as that associated with the jaw joint. Moreover, they have found that dental students can be taught to recognize these facial movement patterns very accurately and to improve their pain control techniques during dental procedures that induce pain or discomfort. Other researchers are pursuing findings suggesting that a specific wave pattern found in the brain responds differently under experimental conditions requiring close vigilance to another task in persons who are experiencing actual pain compared to those feigning pain.

For an estimated 5 to 10 percent of the adult U.S. population, the jaw (temporomandibular) joint and its associated muscles are the site of persisting pain or functional limitations (e.g., problems with chewing or with the jaw "locking" open or shut). Our investigators have demonstrated conclusively that temporomandibular disorders (TMD) include several conditions with fundamentally different etiologies, prognoses, and treatment requirements. They have found that over 75 percent of clinical patients show no apparent joint pathology, but instead show muscle tenderness and hyperactivity, associated in many patients with elevated levels of psychological stress. Some treatments appear to provide substantial relief, although adequate clinical trials verifying their efficacy remain lacking.

To encourage much-needed basic and clinical research on this topic, the Institute will aim several solicitations in FY 1991 toward increasing understanding of joint and muscle pain, inflammatory pain, and pathophysiological and behavioral factors underlying various jaw disorders, as well as determining the efficacy of various diagnostic and therapeutic procedures used.

Many factors--including cultural, behavioral, social, and economic factors--contribute to differences in disease risk among population subgroups. Increased understanding of such risk factors can lead to better approaches for improving health and targeting scarce preventive and health care resources. Because behavior can sometimes be modified, we continue to support research in the identification and development of interventions that can lead to the elimination of this risk factor in oral disease.

National Institute of Dental Research

Intramural Research

Authorization: Indefinite

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
263	$26,995,000	270	$28,567,000	+7	+$1,572,000

Purpose and Method of Operation

Intramural research at the NIDR is conducted in nine laboratories and branches. A dental clinic and a pain research unit are maintained in the NIH Clinical Center to conduct research and diagnostics for certain NIH hospital and outpatients. The Institute's intramural research budget activity also includes a major Epidemiology and Oral Disease Prevention Program.

The individual laboratories and branches of the Intramural Research Program conduct basic and clinical research to improve the diagnosis, prevention, and treatment of dental caries, periodontal and oral soft tissue diseases, including autoimmune diseases and AIDS, oral cancers, developmental abnormalities, disorders affecting cartilage and bone, orofacial pain, and diabetes. The investigative tools employed include biometrics, biochemistry, biology, biophysics, immunology, microbiology, molecular biology, neurophysiology, virology, behavioral science, and clinical dentistry.

Rationale for the Budget Request

The 1991 budget request for intramural research is $28,567,000, an increase of $1,572,000 over the 1990 level. The following descriptions are indicative of the efforts under way and planned:

Clinical Investigations and Patient Care

In Sjogren's syndrome, the salivary and lacrimal glands are believed to be destroyed by the patient's own white blood cells, making the syndrome an "autoimmune" disease. Characteristic changes seen in the saliva of Sjogren's syndrome patients include elevations of electrolytes, certain proteins, and fats. In recent work at NIDR, we have shown that the submandibular glands (those under the tongue) are more severely involved than the parotid glands (those in the cheeks). We have also found that certain "autoantibodies," particularly IgA rheumatoid factor, are good indices of disease activity in these patients. Because little is understood about how the glands become nonfunctional, we are pursuing additional investigations in this area.

Our scientists continue to make major progress in understanding the mechanisms of normal saliva production. Past and present emphasis has been on the neurochemical control of salivary fluid secretion, with particular attention to the intracellular signals that mediate these responses. These studies have already led to novel therapies to treat some forms of Sjogren's syndrome dysfunction. They are also helping to develop models for Sjogren's syndrome that may reveal how the glands become nonfunctional and thus point the way to improved medications.

Most tooth loss is due to dental caries or periodontal disease. Additionally, some toothlessness is related to inherited genetic disorders, such as ectodermal dysplasia. While complete dentures have been used for centuries to replace teeth, for many people the results are less than satisfactory. Dental implants, which are devices permanently placed in the jaw to support artificial teeth, may offer a better solution. Our scientists are conducting longitudinal studies using titanium metal implants in toothless patients. These studies are complemented by collaborative research with basic scientists to elucidate the biological events occurring at the interface between bone and implant. These efforts should dramatically increase the utility and success of dental implants for correction of toothlessness.

Bone Research

Diseases of the skeleton and the dentitition plague man throughout life. Many of these disorders increase in prevalence and severity with advancing age and are now responsible for a major part of the nation's total health bill. Osteoporosis, osteoarthritis, rheumatoid arthritis, dental caries, and periodontal disease are all chronic and debilitating illnesses that directly attack bones, cartilage, and teeth. Inherited diseases of mineralized tissue--osteogenesis (bone), dentinogenesis (dentin), and amelogenesis (enamel) imperfecta--generate deformities and fragility of hard tissues that severely affect thousands of children and their families each year. NIDR scientists study these skeletal and dental diseases at the molecular, cellular and biophysical levels to establish a better understanding of structural and functional defects. The ultimate goal of these studies is to devise new tools and strategies for more effective prevention and therapy of these disorders.

For example, our biologists have shown that physiological levels of either Insulin-like Growth Factor-1 (IGF-1) or Transforming Growth Factor-(TGF-β) used as the only supplement to a simple cell culture medium fully support the viability and steady state metabolism of articular cartilage tissue slices indefinitely. These results are important because they provide a basis to explore the use of specific growth factors to support the normal metabolism of older cartilage tissue, and possibly reverse the damage incurred by such conditions as osteoarthritis.

In past years, NIDR cell biologists devised procedures to isolate and study human bone-forming cells (osteoblasts) from any donor, regardless of of basement membrane in the metastases of tumor cells. Investigators have identified a smaller segment of the laminin molecule involved in these activities, synthesized it, and shown that it can increase tumor cell metastases five-fold in vivo. Exposure of nonmalignant cells to this molecule increases production of the enzyme collagenase IV used to degrade the membrane. Drugs aimed at inhibiting this enzyme should reduce the spread of cancer. Approaches that block enzyme synthesis, inhibit its activity, or prevent tumor cells from interacting with the collagenase-inducing site on laminin are being tested in experimental animals and are found to greatly reduce tumor spread.

Blood vessel formation is an important process during development, in tissue repair after injury, and in supplying nutrients to malignant tumors. New information about the factors that regulate the formation of blood vessels has been gained from cell culture studies. We have developed an in vitro model of blood vessel formation using cells that line the umbilical cord. It may now be possible to develop new approaches to increasing blood vessel formation (such as after a heart attack) or to decreasing blood vessel formation (in conditions such as diabetic retinopathy and Kaposi's sarcoma).

NIDR scientists were the first to show that the basement membrane molecule, laminin, is a potent stimulator of nerve fiber outgrowth. We have now completely cloned and sequenced laminin, and have identified an active site that promotes neurite outgrowth. The possible use of this peptide in both the linear and more stable polymerized form for in vivo repair studies is being investigated. Advantages of the peptide are its high activity, low antigenicity, and ready availability.

Cartilage is a highly specialized connective tissue rich in extracellular fibrous material and other components that form a matrix enabling the tissue to absorb shock and resist compression at the body's joints. A number of inherited and acquired diseases are associated with cartilage defects, including chondrodysplasia, rheumatoid arthritis, and osteoarthritis. These diseases may be caused by defects in the cartilage matrix and/or abnormal synthesis of matrix components. NIDR scientists have cloned several genes for major cartilage components such as collagen, and proteoglycan, and have studied how these genes are regulated in normal development and in disease. Several patients with spondyoepiphyseal dysplasia congenita, a form of dwarfism, have been found to have a defective cartilage collagen gene.

In other studies, NIDR investigators are using transgenic mouse models to study how genes associated with the regulation of cartilage growth may be involved in the development of the inflammation and joint weakness associated with arthritic conditions.

NIDR scientists are studying diabetes because diabetic patients are susceptible to periodontal disease. However, the major problems for patient survival and quality of life continue to be related to diabetic kidney failure. In the United States alone, more than 50 percent of the 75,000 patients carrying the diagnosis of end-stage renal disease are thought to have kidney failure due to diabetes. The entitlement programs that support these patients cost the taxpayer well over $2 billion each year.

In previous studies of experimental diabetes, we have shown increased amounts of a substance produced by the kidney (thromboxane) that constricts blood vessels and induces clumping of platelets, the blood factors involved in clotting. Because one of the most prominent features of diabetic kidneys is thickening of the membrane that acts as the filtration barrier, our scientists have evaluated the effects of thromboxane on the expression of the genes that produce the membrane proteins. They have found that thromboxane activates production of these proteins; thus, increased production of thromboxane may lead to progressive renal failure. Since antagonists for thromboxane are available experimentally and have very low patient toxicity, these studies provide a potentially exciting and new form of therapy for the complications of diabetes.

Immunology

Many chronic inflammatory conditions such as periodontal disease, rheumatoid arthritis, and tuberculosis are associated with altered immune responses that contribute to the pathology of the disease. Recently, we identified a product of activated inflammatory cells that contribute to this immunosuppression. The immunosuppressive potential of the peptide, transforming growth factor beta (TGF-), was demonstrated for the first time in an experimental animal model in which chronic inflammation was induced by bacterial products. Moreover, recent evidence indicates that this growth factor is also present in the joint membrane of patients with chronic rheumatoid arthritis and in the oral tissues associated with periodontal disease. These observations have prompted a new initiative to explore the role of this peptide in the pathogenesis of periodontal disease.

Cellular Development and Oncology

Over the last several years, "proto-oncogenes," which are normal genes of the human genome, have been implicated in the development of cancer. Normally, these genes are involved in orderly processes of growth and development. Under certain circumstances, however, these genes may be activated to induce cells to proliferate at the wrong time or place in the body, initiating an important step in the conversion of normal cells to malignant ones. In addition, recent evidence has suggested that not all proto-oncogenes contribute to cancer development by stimulating cell division. Most recently, our investigators have shown that the protein product of a particular proto-oncogene is found in mature but not in immature human white blood cells (neutrophils) and that this protein moves from intracellular granules to the cell surface when the neutrophil is activated. These findings represent the first functional evidence that proto-oncogenes act in pathways not related to cell growth and suggest the existence of new mechanisms leading to malignant conversion.

Osteogenin, a bone differentiation factor discovered by NIDR scientists, was isolated and purified in the NIDR intramural laboratories. Now, human osteogenin has been cloned by recombinant DNA methodology, an advance that will enable us to explore the potential of osteogenin as an essential factor been used to diagnose bone loss in two longitudinal studies of periodontal disease in adolescents.

Understanding the determinants of tooth loss is essential for the identification of individuals and groups at high risk and for effective interventions to reduce tooth loss among persons where it remains a problem. The objective of a new NIDR project is to measure tooth loss and its determinants in the natural settings of dental offices and larger public clinics. Information will be collected regarding the influence of clinical conditions, economic variables, patient/provider characteristics, and attitudes on decisions to extract permanent teeth. The collected data will be used to assess the significance of factors contributing to the loss of permanent teeth in the United States. With these data, a more complete model of tooth loss than is currently available can be developed.

National Institute of Dental Research

Research Management and Support

Authorization: Indefinite

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
78	$9,303,000	89	$9,900,000	+6	+$597,000

Purpose and Method of Operation

This activity provides the leadership and management direction of the entire Institute in addition to the administrative management and scientific direction in the review, award, and monitoring of all extramural awards. Associated with this activity is the immediate Office of the Director and the Institute's scientific and administrative staff.

This activity will continue to provide the leadership, program guidance, planning and evaluation, and overall administration for the programs and information directed to scientists, dental practitioners, and the public, in addition to continuing to administer, manage, and review the Institute's grant and contract programs.

Rationale for the Budget Request

The 1991 request for research management and support is $9,900,000, an increase of $597,000 over the 1990 level.

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Detail of Permanent Positions

	1989 Actual	1990 Appropriation	1991 Estimate
ES-60	2	3	3
ES-61	3	3	3
Subtotal	5	6	6
GS/GM-15	18	18	19
GS/GM-14	27	27	27
GS/GM-13	16	16	16
GS-12	18	19	21
GS-11	23	25	27
GS-10	1	1	1
GS-9	21	24	26
GS-8	10	10	10
GS-7	27	30	34
GS-6	13	14	15
GS-5	12	13	15
GS-4	2	2	2
GS-3	3	3	3
Subtotal	191	202	216
Grades established by Act of July 1, 1944 (42 USC 207):			
Assistant Surgeon General	1	1	1
Medical Director	2	2	2
Director Grade	18	18	18
Senior Grade	1	1	1
Full Grade	1	1	1
Subtotal	23	23	23
Ungraded	5	5	5
Total permanent positions	224	236	250

NATIONAL INSTITUTES OF HEALTH

National Institute on Dental Research

New Positions Requested

		1991	
Intramural Research	Grade	Number	Annual Salary
Statistician	GS-15	1	$ 61,289
Microbiologist	GS-12	1	37,079
Chemist	GS-11	1	30,937
Biologist	GS- 9	1	25,570
Biologist	GS- 7	1	20,902
Administrative Specialist	GS- 7	1	20,902
Secretary	GS- 6	1	18,810
Secretary	GS- 5	1	16,876
		8	232,365
Program Support			
Program Analyst	GS-12	1	37,079
Grants Management Specialist	GS-11	1	30,937
Administrative Specialist	GS- 9	1	25,570
Grants Technical Assistant	GS- 7	1	20,902
Secretary	GS- 7	1	20,902
Clerk Typist	GS- 5	1	16,876
		6	152,266

NATIONAL INSTITUTES OF HEALTH

National Institute of Dental Research

Advisory and Assistance Services

For FY 1991, the Advisory and Assistance Services budget will be $107,000, an increase of $4,000 over the FY 1990 level. These funds will continue to provide a variety of contractual, support, and advisory services to the Institute, as follows:

Contractual services with individuals are necessary to provide for specialized ad hoc advisory support in areas not otherwise represented by NIDR staff or the regularly appointed membership of NIDR advisory groups. Such procurement is more economical than hiring permanent staff for short-term or highly specialized efforts.

Management and professional support services are required to provide specialized knowledge and expertise to advise, review, and evaluate the administration and management of the Institute's programs. Such activities are integral to the effective planning and management of the NIDR and bring a non-Federal perspective to this area.

The personnel appointment mechanism is used to bring the various advisory committees to the NIDR: the National Advisory Dental Research Council, the Program Advisory Committee, and the Board of Scientific Counselors. The members of these groups review grant applications and contract proposals and recommend approval or disapproval of funding, review and evaluate the intramural and extramural programs of the Institute, and provide expert advice and recommendations related to the development and conduct of specific research activities. The appointed members of the congressionally mandated Council perform services that are essential to the review process; by statute, their concurrence is required before most grant awards can be made.

To ensure appropriate use of consulting services, the NIDR has established a review procedure involving all appropriate administrative and management personnel. Proposals are reviewed by the pertinent Administrative Officers, the Committee Management Officer, the Budget Officer, the Executive Officer, appropriate program managers, and the NIDR Deputy Director and/or Director as necessary.

WEDNESDAY, MARCH 14, 1990.

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASE

WITNESSES

DR. PHILLIP E. GORDEN, DIRECTOR, NIDDK
DR. WILLIAM F. RAUB, ACTING DIRECTOR, NIH
L. EARL LAURENCE, EXECUTIVE OFFICER, NIDDK
DONALD F. CYPHERS, FINANCIAL MANAGEMENT OFFICER, NIDDK
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. NATCHER. At this time we take up the budget request for the National Institute of Diabetes and Digestive and Kidney Diseases. We have before the committee Dr. Gorden.

Dr. Gorden, before you give us your statement, tell us who you have with you there at the table.

Dr. GORDEN. Mr. Chairman, on my far left, Mr. Donald Cyphers, our Budget Officer; on my immediate left, Mr. Earl Laurence, our Executive Officer; and I believe you know the gentleman to my right.

OPENING REMARKS

Mr. NATCHER. We are delighted to have all of you before the committee at this time. Now, Dr. Gorden, we would be glad to hear from you.

Dr. GORDEN. Thank you very much, Mr. Chairman.

Forty years ago President Harry S. Truman signed the law creating our Institute. In recognition of our 40th anniversary, I would like to focus on four research areas in which this Institute has made special contributions: cystic fibrosis, diabetes, kidney disease, and liver disease.

The progress in these areas exemplifies the crucial importance of this Institute's world premiere basic research which has laid the foundation for landmark advances in biotechnology, drug and device development and clinical procedures.

One of the crowning research achievements of the past year was the discovery of the gene for cystic fibrosis.

Figure 1 highlights major events in the cystic fibrosis research story. In 1953, Dr. Paul Di Sant'Agnese, an NIDDK intramural scientist, discovered an abnormality in the sweat of cystic fibrosis patients. This advance led to the first diagnostic test for the disease.

This was followed by three key Nobel prize-winning discoveries that took place in our intramural laboratories. In 1956, Arthur Kornberg discovered the mechanism by which the genetic material, DNA, replicates itself. In 1960, Christian Anfinsen discovered the mechanism used by proteins to fold themselves into their proper shapes. In 1964, Marshall Nirenberg spearheaded the unraveling of the genetic code through which DNA translates itself into the protein building blocks of the body.

Finally, in 1989, a team of NIDDK-supported American and Canadian scientists pinpointed the gene. It is now possible in the laboratory to repair defective genes and gene products, and to use these techniques to understand genetic diseases and hopefully, in the near future treat them.

The next figure, figure 2, shows the diabetic athlete, Wade Wilson, who is the current starting quarterback for the National Football League's Minnesota Vikings. When this Institute was founded, the idea of a diabetic quarterback was unimaginable. Diabetes was then a physically and mentally debilitating disease.

The discovery of insulin in the 1920's helped prolong the lives of diabetics, but we understood very little of the disease process, and of the severe complications that lead to kidney disease, blindness, and nerve damage. Over the past 40 years our ability to comprehend and manage diabetes has changed dramatically.

Today, we know that diabetes, which affects an estimated 12 million Americans, isn't just one disease with one cause, but several genetic diseases. In Type I or insulin-dependent diabetes, the body's immune system mistakenly destroys the special group of cells that produce insulin. There is a major genetic risk to this condition. We know at least one error in DNA that marks this risk. For Type II diabetes, resistance to insulin is the underlying problem. Genetics plays a crucial role here, too, and there is a strong association with obesity. This type of diabetes disproportionately affects our Black, Hispanic, and Native American populations.

Figure 3 shows some key advances in improving the diagnosis and clinical management of diabetes. An innovative computer package now allows doctors to analyze and adjust a patient's treatment. An insulin delivery pump provides an alternative to daily insulin injections. We brought one of these pumps with us today as an example to show you. This pump is commercially available, but research is continuing on other experimental pumps that would be even more efficient in delivering insulin and offer alternatives to daily injections. Recombinant human insulin is now available as a result of biotechnology. Also, small and easy-to-use devices can test blood sugar at home or at work.

When the NIDDK was founded in 1950, there was nothing to offer as a treatment for end-stage kidney disease. Patients with kidney failure often died within weeks. Now three major advances have completely altered the outlook for end-stage renal disease patients. The first is dialysis, which successfully maintains even those whose kidneys are useless. Figure 4 contrasts the early dialysis machines with the more modern, convenient equipment of today.

The second advance in treating end-stage renal disease is the drug erythropoietin, a natural body hormone that is produced by biotechnology. It combats the anemia of dialysis patients and allows many of them to return to work and lead full and productive lives.

A third major advance in end-stage renal disease has been kidney transplantation. Figure 5 shows a little boy before and after a kidney transplant. About 50 percent of end-stage renal disease patients will eventually receive a transplant and will recover to lead normal lives. Success rates for kidney transplantation have increased steadily, with the one year graft survival rate for a transplant from a living related donor now approaching 90 percent.

A similar story can now be told for liver transplantation. Figure 6 points out that over two-thirds of liver transplant recipients survive a year after transplantation, and this survival rate is rapidly approaching three years. Transplantation as a treatment for liver disease has developed entirely during the history of the NIDDK, which for over 20 years has supported one of the premiere researchers in this field, Dr. Thomas Starzl of the University of Pittsburgh.

Figure 7 shows one of Dr. Starzl's patients, a 42-year-old minister from California. He received a donor liver in 1987 due to chronic active hepatitis he acquired while serving in Vietnam. This figure shows the patient at the time of the operation, in contrast to the healthy adult he was one year later, and that he continues to be today.

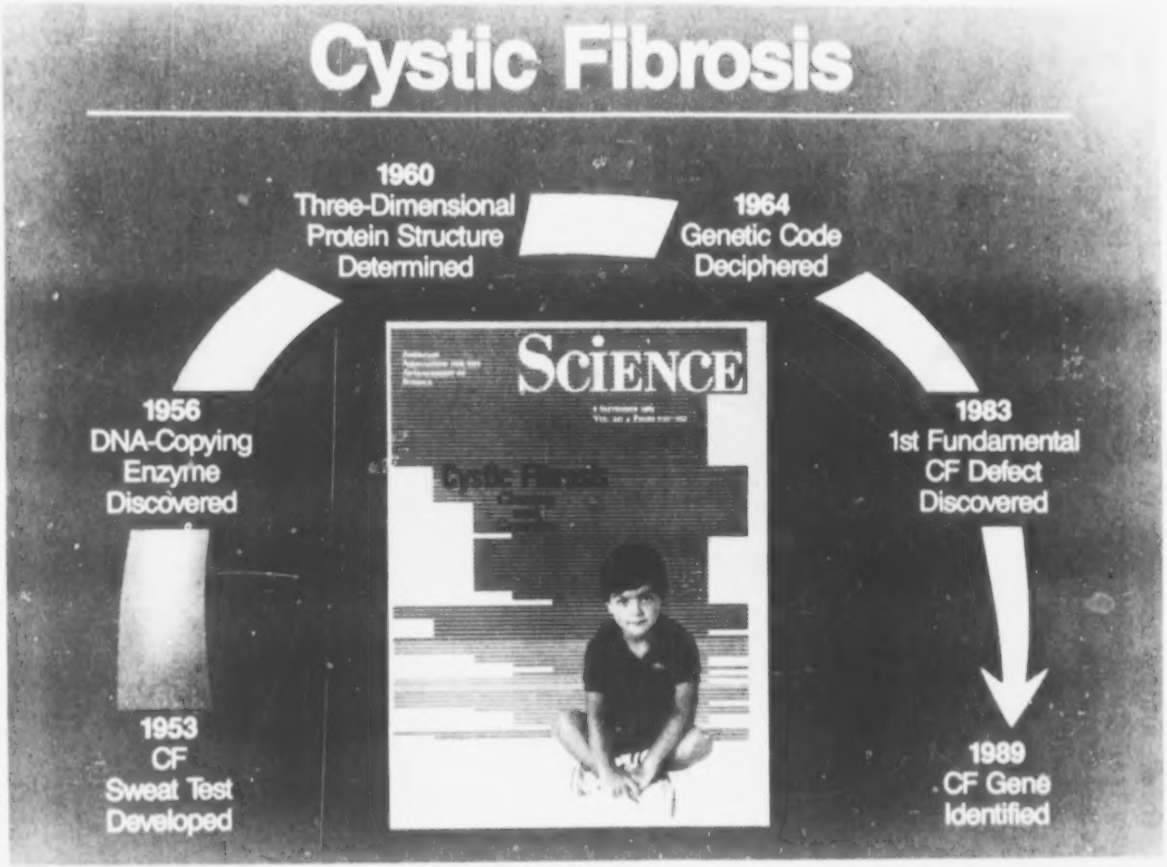
While dialysis and the transplantation of kidneys and livers are life-saving therapies, we must remember that they are still halfway technologies that do not address the underlying causes of disease. For this reason, the NIDDK is firmly committed to pursuing research aimed at preventing these chronic and costly diseases. In this regard, I am pleased to report that an intramural scientist has recently developed a promising treatment for Type C hepatitis, which accounts for the vast majority of the cases of post-transfusion hepatitis and can cause cirrhosis, followed by liver failure.

I have chosen today to present only a few of the major areas of research to illustrate the achievement of our Institute over its 40-year history. In looking to the future, I hope soon to be able to tell you more about other diseases that we are now only beginning to understand, diseases such as inflammatory bowel disease, obesity, osteoporosis, interstitial cystitis, and polycystic kidney disease.

We knew virtually nothing about these diseases 40 years ago. Now; they are being characterized and research is under way to apply to these diseases the same techniques that have proven so successful in cystic fibrosis. The foresight of the Congress and the public in strongly supporting the work of the Institute during the past 40 years has resulted in major health advances for the American people. Your continued faith in our efforts and support for our mission can lead to improved health and well-being for millions more.

Mr. Chairman, the 1991 budget request for the National Institute of Diabetes, and Digestive and Kidney Diseases is $605,349,000. Thank you very much for your attention. I will be very pleased to answer any questions that you have.

[The charts and the prepared statement of the Director, National Institute of Diabetes and Digestive and Kidney Diseases follow:]



Cystic Fibrosis

1953
CF
Sweat Test
Developed

1956
DNA-Copying
Enzyme
Discovered

1960
Three-Dimensional
Protein Structure
Determined

1964
Genetic Code
Deciphered

1983
1st Fundamental
CF Defect
Discovered

1989
CF Gene
Identified

Figure 1.

Diabetes
Quarterback Wade Wilson
CALLING THE PLAY AGAINST DIABETES
11
76
58
GROUP THERAPY: STRENGTH IN NUMBERS
COMPUTERS

Figure 2.

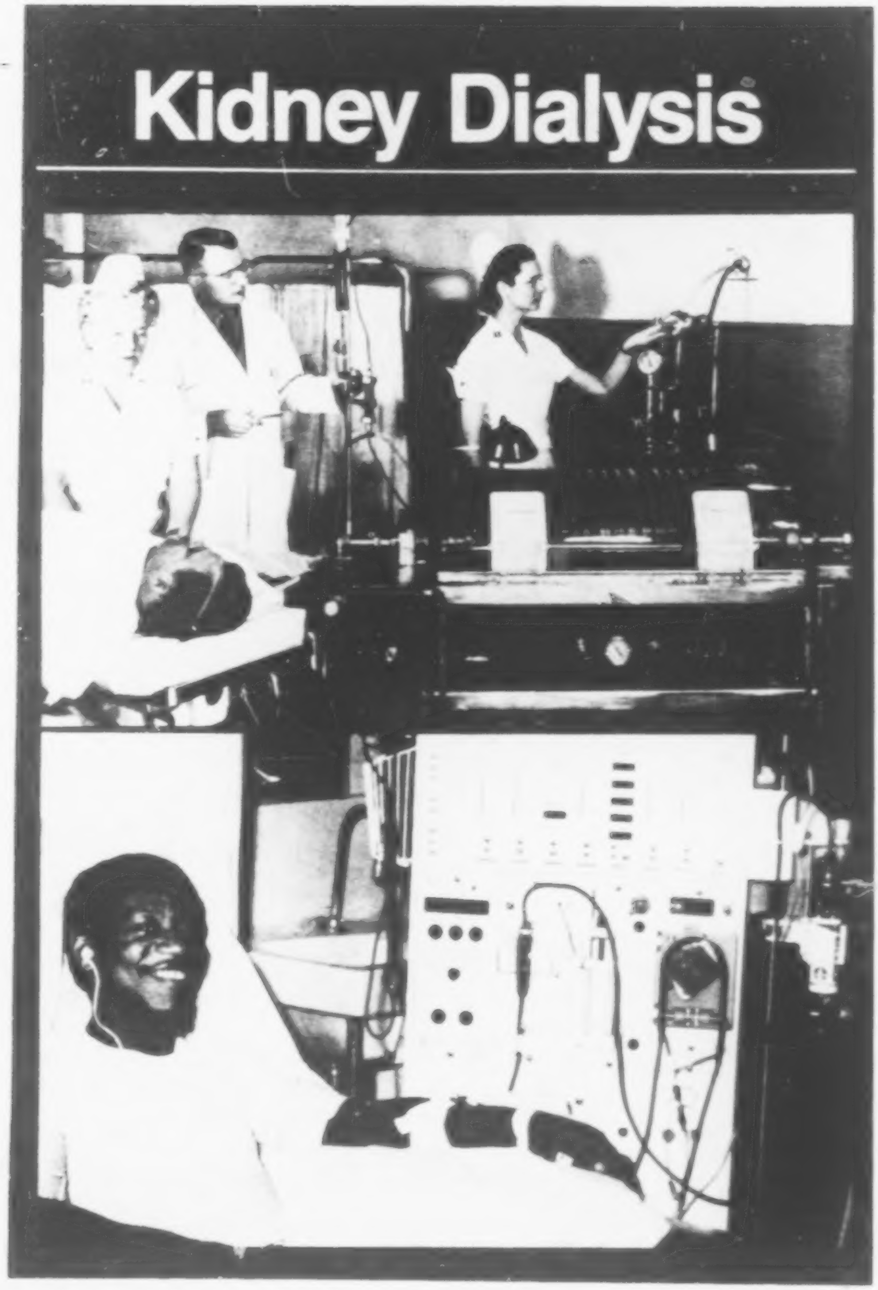

Kidney Dialysis

Figure 4.

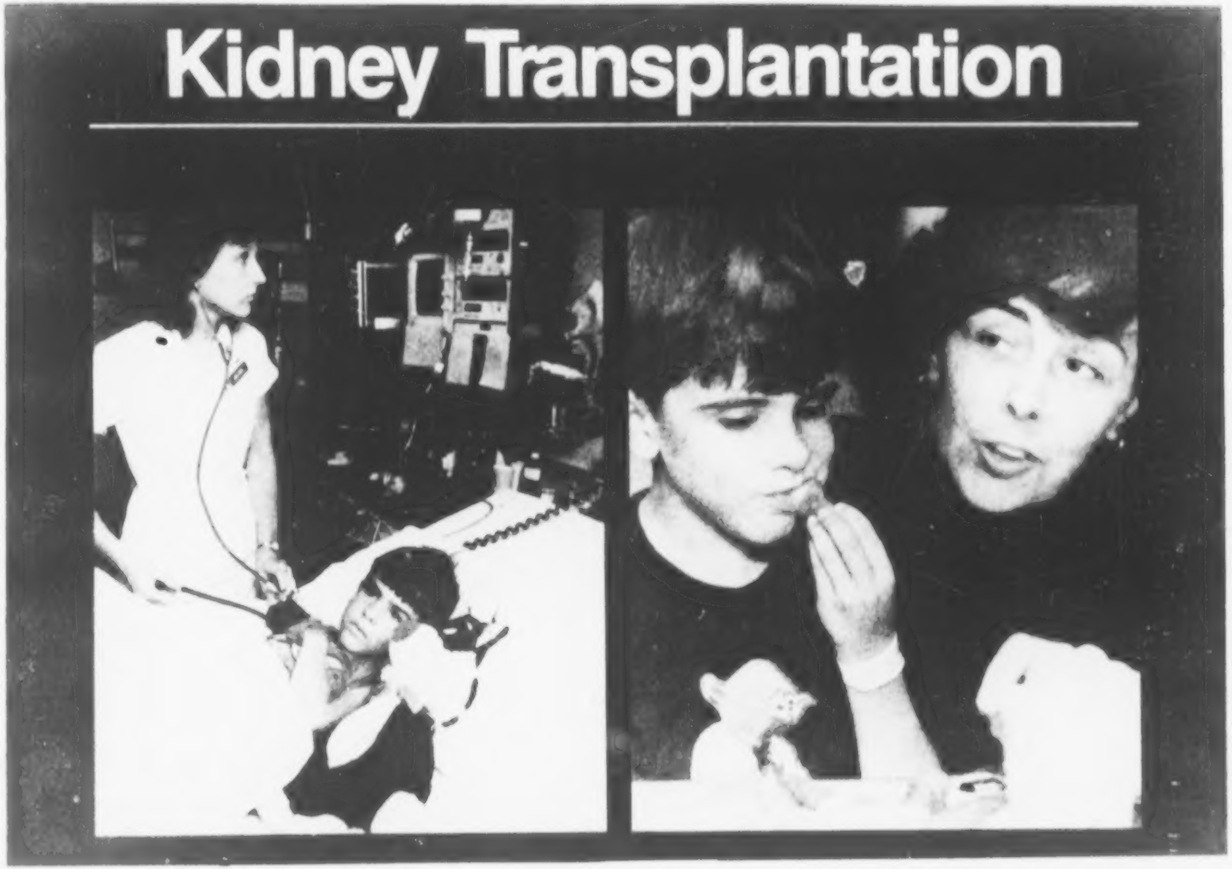

Kidney Transplantation

Figure 5.

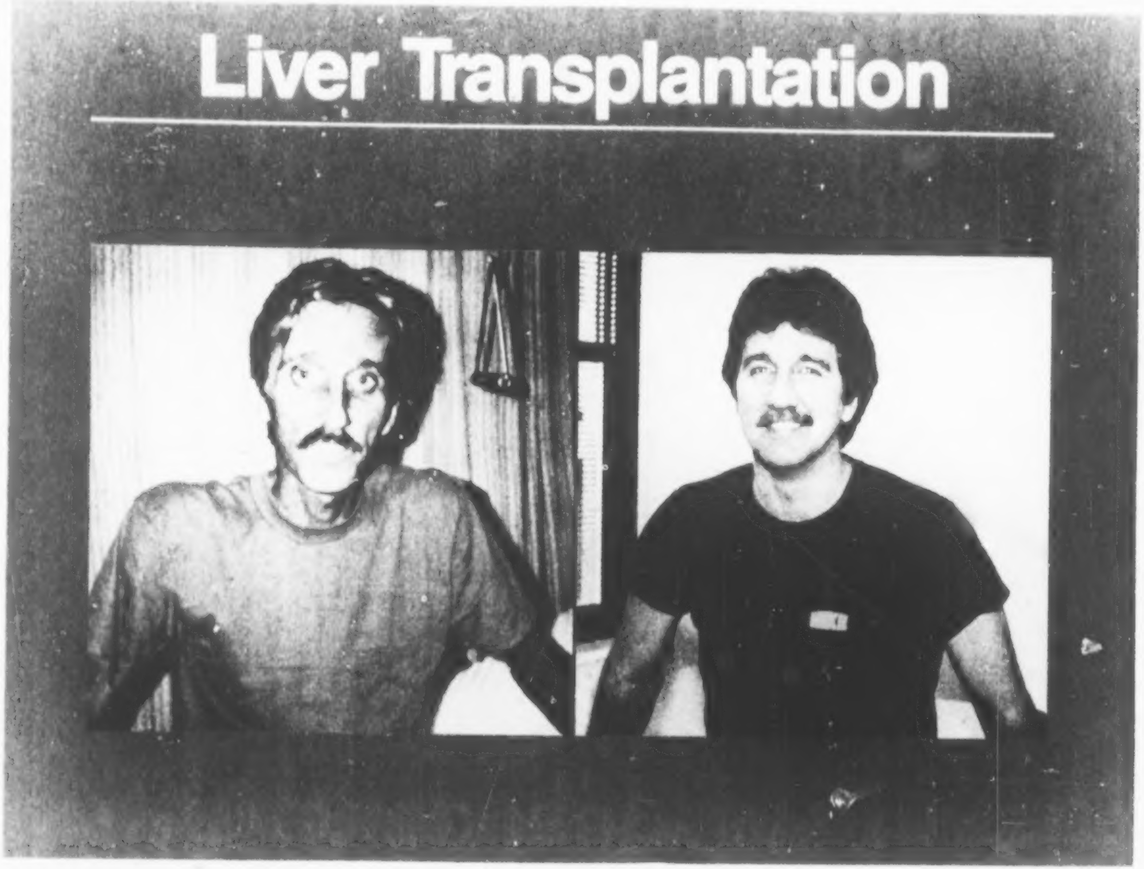

Liver Transplantation

Figure 1.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute of Diabetes and Digestive and Kidney Diseases

I am particularly pleased to be able to testify before the Subcommittee in 1990, the year that the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) celebrates its 40th anniversary. In recognition of this milestone, I would like to focus on four research areas in which this Institute has made major contributions during the past 40 years: cystic fibrosis, diabetes, kidney disease, and liver disease. The progress in these areas exemplifies the crucial importance of this Institute's solid basic research, which has laid the foundation for landmark advances in biotechnology, drug and device development, and clinical procedures.

For 40 years, NIDDK has been in the vanguard of research on cystic fibrosis, a disease that painfully strikes down and kills children and young adults. Thus it is with a profound sense of accomplishment that we can report the recent discovery of the defective gene and protein responsible for the most prevalent form of this dread disease. This is one of the crowning research achievements of the past year, and the culmination of decades of basic research supported through the collective efforts of several NIH institutes, the Howard Hughes Medical Institute, and the CF Foundation.

Prior to 1950--the year this Institute was created--cystic fibrosis was one of the most hopeless diseases known. At that time, Arthur Kornberg was a brilliant young biochemist working in a laboratory at the NIH that is now part of the NIDDK intramural research program. In 1956, he discovered the first enzyme known that could copy DNA, the cellular material that is the key to modern molecular biology and genetics. At the time, no one thought this finding had any bearing on cystic fibrosis, but in many ways, Kornberg's work was a precursor of today's recombinant DNA technology, which enabled the discovery of the cystic fibrosis gene. Kornberg went on to receive the Nobel prize for his seminal achievement--the first in a series of Nobel laureates who have roots in the NIDDK.

Another important benchmark in CF research was in 1953, just three years after this Institute was formed. Paul Di Sant'Agnese, an NIDDK scientist, discovered an abnormality in the sweat of cystic fibrosis patients. This advance led to the first diagnostic test for this disease. In the following years, NIDDK researchers were at the hub of the revolution in molecular biology that later proved essential to the discovery of the CF gene. Marshall Nirenberg spearheaded the unravelling of the code through which DNA translates itself into the protein building blocks of the body. Christian Anfinsen uncovered the mechanism used by proteins to fold themselves into their proper shapes. These scientists won Nobel prizes for their ground-breaking work--work that needed to be accomplished before the secret of cystic fibrosis could be revealed.

Then, in 1983, NIDDK-supported researchers, who were engaged in pioneering studies of cell membranes, discovered the first fundamental molecular defect in cystic fibrosis. They found that the channels transporting salts through cell membranes in CF patients did not work correctly. These studies helped to explain the debilitating mucus that impedes the proper functioning of the lungs, the digestive system and the pancreas in CF patients.

In 1987, NIDDK grantees pinpointed the location of the CF gene to a specific chromosome, and research teams around the world began to narrow their search. Finally, in 1989, a team of NIDDK-supported American and Canadian scientists reported how they had "walked" and "jumped" up and down the chromosome to pinpoint the gene in an approach called "reverse" genetics. In conventional genetics scientists find the defective protein first and work from there to find the gene. In "reverse" genetics, they find the gene first. For the CF researchers, this approach was likened to looking for a broken faucet in a house somewhere in the United States, without the benefit of road maps. Fortunately, with the tools of modern molecular biology, they succeeded.

The discovery of the CF gene rests solidly on years of prior work in cell biology that has developed in a parallel track with molecular genetics. Such fundamental, untargeted research has relied for decades upon the support of the Congress and the public. Now, armed with the CF gene, researchers can design membrane study systems to find ways to make the defective protein work correctly, and ultimately, to seek ways to correct the genetic defect in CF patients through gene therapy. We used to call cystic fibrosis a "disease in search of an idea." In 1990, it is a disease for which there is renewed hope and intense research momentum.

The achievement record in diabetes research is similarly impressive, in terms of understanding and managing this disease. Forty years ago, when this Institute was founded, diabetes was an enigma. The discovery of insulin in the 1920s helped prolong the lives of diabetics, but we understood very little of the disease process and of the severe complications that plagued patients: heart and nerve damage, amputations, and blindness. Over the past 40 years, our ability to comprehend and manage diabetes has changed dramatically. Today, we know that diabetes, which affects an estimated 11-12 million Americans, isn't just one disease with one cause. We know that in Type I, or insulin-dependent diabetes, the body's immune system mistakenly destroys the special group of cells that produce insulin. There is a major genetic risk factor for this condition--and we know at least one error in DNA that marks this risk. For Type II diabetes, we know that resistance to insulin is the underlying problem. Genetics plays a role in causing this disease, but life-style risk factors such as obesity also are extremely important. We also know that Type II diabetes disproportionately affects the Black, Hispanic, Native American, Alaska Native and Native Hawaiian populations.

Major advances have also been attained in improved diagnosis and clinical management of diabetes. Today, if you have diabetes, the chances are greater that you have been diagnosed early. This is important in receiving proper medical advice and treatment, especially for anticipating and treating diabetic complications. While insulin shots are still part of the daily routine of many patients, recombinant human insulin is now available as a result of biotechnology. This drug has prevented problems of insulin shortage, contamination, and immune reaction related to the animal products that were previously the only source of insulin. Today, patients can also conveniently test their blood at home or work to see if they need more insulin --making it far less likely that they will take too much and risk a coma. Recently, the development of an implantable insulin pump has progressed to successful testing for an 18-month period. When the appropriate research on this device is concluded, the pump will offer patients a treatment option that frees them from daily shots, although they must continue to monitor their blood glucose levels. These clinical management techniques are important to patients and their families, empowering them to take control of their disease and live more productive and unencumbered lives.

Another critical advance in diabetes has been the ability to test patients for molecules in their blood that form when glucose levels stay too high over time. This is vital information in monitoring the treatment of a diabetic patient--to know when that person is succeeding in controlling glucose levels, and when he or she needs help. The NIDDK is sponsoring a large multicenter clinical trial to answer the single most important clinical question in diabetes today--whether long-term careful control of blood glucose levels as close to normal as possible can prevent, delay, or ameliorate the development of the blood-vessel damage that is a major complication of diabetes.

During the past 40 years of this Institute's achievements, another example of major research progress has been end stage renal disease (ESRD). When the NIDDK was founded in 1950, there was nothing to offer as a treatment: patients often died within days or weeks of acute kidney failure. Now, three major advances have completely altered the outlook for ESRD patients. The first is dialysis, which can successfully maintain even those patients whose kidneys are useless. Initially, this life-saving procedure was cumbersome and time-consuming. Today, however, kidney dialysis can be performed comfortably and relatively quickly in hospitals, dialysis centers, and at home.

A second advance in ESRD is the approval by the Food and Drug Administration of a new drug that combats the anemia of dialysis patients and enables many of them to return to work and lead full and productive lives. This drug, called erythropoietin, was developed through the new techniques of biotechnology, with research supported in part by this Institute. The drug stimulates the production of red blood cells, thereby allowing dialysis patients to overcome the anemia and exhaustion that often afflict them.

A third advance in ESRD is kidney transplantation. About 50 percent of ESRD patients will eventually receive a transplant. The success rates for this procedure have increased steadily during the years, with the one-year graft survival rate for a transplant from a living-related donor now approaching 90 percent. This Institute has contributed greatly to the development of new transplantation approaches by transplant surgeons and urologists. These advances have in turn helped the development of the nation's organ donor system, which provides needed organs for ESRD patients, as well as an opportunity for people to help each other in fighting disease.

This retrospective on the 40-year accomplishments of the NIDDK would be incomplete without a description of our efforts to combat liver failure. Forty years ago, liver failure was an absolute death sentence. Today, over two thirds of transplant recipients survive a year or more after transplantation and the long-term survival rate continues to improve. Transplantation as a treatment for liver disease has developed entirely during the history of the NIDDK, which for over 20 years has continuously supported one of the premiere researchers in the field, Dr. Thomas Starzl of the University of Pittsburgh.

New drugs and new surgical techniques have transformed liver transplantation from an experimental procedure to a successful treatment. The development of the immunosuppressant drug, cyclosporine, has played a key role in this progress. Recently, a new drug called FK-506 has demonstrated great promise for protecting against transplant rejection, but without the side effects of cyclosporine. Another central advance in liver transplantation has been the development, with NIDDK support, of a solution for preservation of donor organs until they can be transplanted. This solution has made it possible to maintain organs outside the body for much longer periods of time, thereby enabling greater use of available organs and better matches of donor and recipient. The solution is expected to improve graft viability in other forms of transplantation as well.

While kidney dialysis and the transplantation of kidneys and livers are life-saving therapies, we also have to remember that they are still "half-way" technologies that do not address the underlying causes of disease. For this reason, the NIDDK is firmly committed to pursuing research aimed at preventing these chronic and costly diseases. I'm pleased today to be able to report from the Institute's intramural program a recent major research advance in the treatment of liver disease. For the first time, a promising treatment has been discovered for Type C hepatitis, which accounts for the vast majority of the cases of post-transfusion hepatitis, and can cause cirrhosis followed by liver failure and transplantation. Fifty percent of patients with chronic hepatitis C showed a complete response when treated with recombinant alpha interferon administered in a randomized, controlled clinical trial. We are energetically pursuing this significant discovery in order to examine long-term responses and to evaluate the combined use of alpha interferon with other agents.

I have chosen today to present only a few major areas of research to illustrate the achievements our Institute has supported over most of its 40-year history. In looking to the future, I hope soon to be able to tell you more about other diseases that we are only just beginning to understand--diseases such as inflammatory bowel disease, interstitial cystitis, and polycystic kidney disease. We knew virtually nothing about these diseases 40 years ago. Now, they are being characterized, and research is under way to apply to these diseases the same techniques of molecular biology that have proven so successful in cystic fibrosis. We are also actively pursuing promising research leads on a wide range of other important public health problems such as osteoporosis and obesity.

The foresight of the Congress and the public in strongly supporting the work of the NIDDK during the past 40 years has resulted in major health advances for the huge population of Americans afflicted with chronic diseases. Your continued faith in our efforts and support for our mission can lead to improved health and well-being for millions more.

Mr. Chairman, the 1991 budget request for the National Institute of Diabetes and Digestive and Kidney Diseases favors basic research and totals $605,349,000. Thank you for this opportunity to testify.

Phillip Gorden, M.D.
Director, National Institute of Diabetes and Digestive and Kidney Diseases

December 22, 1934. Baldwyn, Mississippi. Married, two children.

Education: B.A., Vanderbilt University, Nashville, Tennessee, 1957; M.D., Vanderbilt University School of Medicine, Nashville, Tennessee, 1961.

Professional History: 1961-62, Intern, Yale University, New Haven, Connecticut. 1962-64, Assistant Resident, Yale University, New Haven, Connecticut. 1964-65, USPHS Clinical Fellow in Metabolism, Yale University, New Haven, Connecticut. 1965-66, USPHS Research Fellow in Metabolism, Yale University, New Haven, Connecticut. 1966-74, Senior Investigator, Clinical Endocrinology Branch, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health. 1974-78, Senior Investigator, Diabetes Branch, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health. 1974-76, Clinical Director, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health. 1976-78, Visiting Professor, Institute of Histology and Embryology, University of Geneva School of Medicine, Geneva, Switzerland. 1978-present, Chief, Section on Clinical and Cellular Biology, Diabetes Branch, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health. 1980-1986, Clinical Director, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health. 1983-1989, Chief, Diabetes Branch, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health. 1986-present, Director, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

Professional Organizations: American College of Physicians, American Diabetes Association, American Federation of Clinical Research, American Society for Clinical Investigation, Endocrine Society, American Society for Cell Biology, Association of American Physicians, American Society for Biochemistry and Molecular Biology.

Honors, Awards: Alpha Omega Alpha Medical Fraternity, 1961. Doctor of Medicine (Honoris Causa) - University of Geneva, Geneva, Switzerland, 1986. Public Health Service Distinguished Service Medal, 1986. Public Health Service Commendation Medal, 1988. Distinguished Alumnus Award and Medal, Vanderbilt Medical School, 1990.

FUTURE DIRECTION IN RESEARCH

Mr. NATCHER. Dr. Gorden, as you have mentioned to the committee, this is the 40th anniversary of the Institute. You have described an impressive set of past accomplishments. What do you expect to add to this list to talk to us about on your 50th birthday? Mr. Conte and I will be here and we hope Mr. Early and Mr. Stokes stay with us.

What do you think about the 50th anniversary now, Doctor?

Dr. GORDEN. Well, first of all, Mr. Chairman, it would be a great pleasure for me to be able to make my opening statement to you personally and to your colleagues on our 50th anniversary.

I do plan to be here.

Mr. NATCHER. Good.

Dr. GORDEN. I think what I would like to tell you at our 50th anniversary is that we have clearly provided new hope for the American people based on really solid scientific success. The solid success of the science of today, I believe, will translate into the determination of causes and cures for major chronic diseases such as diabetes, digestive diseases, endocrine disease, nutritional diseases and our major kidney, urologic and hematologic diseases.

I think we will have a very interesting and important story to tell you at our 50th anniversary.

Mr. NATCHER. Now, Doctor, what has the discovery of the cystic fibrosis gene meant in the short run for individuals with this disease?

Dr. GORDEN. I think that the first and perhaps the most important thing is that this is a disease that for many years was without any real hope in terms of treatment. I think the discovery of the gene has added an enormous sense of hope to people who have cystic fibrosis.

First of all, in the laboratory, scientists are enormously excited about research progress. We now know the gene; we now know at least what protein is involved. We don't know exactly what the protein does, but we can create this in the laboratory.

That allows for enormous opportunity to study this disease. It allows for the possibility of repairing this gene, and as genetic therapy moves along, as it is beginning to move at a very rapid pace, there is a real opportunity to repair this process now for individuals who have this disease.

But perhaps even more immediate will be the opportunity to apply drugs or other types of reagents to this particular protein that we can characterize in such detail. So, it is really a discovery of enormous importance.

GENETIC RESEARCH

Mr. NATCHER. How much of your Institute's work and your budget is related to studies which are principally genetic in their focus, Doctor?

Dr. GORDEN. The support for work related to genomic research, that we categorize in that area, is approximately $34,500,000 in 1990 for genomic research in general and approximately $19,000,000 for human genomic research.

Mr. NATCHER. How will your genetics program be affected by the creation of a separate budget and organizational structure for genomic activities?

Dr. GORDEN. Well, I think the most important point to make is that our Institute, as well as our other sister Institutes, will continue to be involved in disease-related genomic research, and we will continue to be the major focus for such disease-related research.

I think the cystic fibrosis gene is one of the very best examples, but there are multiple other examples of the understanding of how genes are regulated, which is really fundamental to the understanding of all biology. That will continue to be a process in our Institute and in other Institutes. I think, hopefully, that process will not be impaired in any way by any other program that is recently inaugurated.

DIABETES GENE

Mr. NATCHER. Doctor, we understand that you will be hosting a meeting this week on efforts to isolate a specific genetic defect which may be critical for efforts to control diabetes. What can you tell us about this meeting?

Dr. GORDEN. We know now and have known for some time that diabetes is not one disease, as we pointed out, but it is more than one disease.

In the insulin-dependent form of diabetes, we have identified a specific genetic susceptibility marker; that is, this particular gene is necessary but not completely sufficient to cause the disease. In the noninsulin-dependent form of diabetes, as we have mentioned, the form that affects our minority populations in such an enormously disproportionate way, there is even a greater genetic focus. This has been highlighted by the fact that, if you have an identical twin with noninsulin-dependent diabetes, within five years the chances that the second twin will develop the same disease is 90 percent.

In other words, there is a 90 percent concordance rate in these genetically identical individuals. This is a very powerful genetic argument. We don't know what genes are involved, but the purpose of this meeting is basically to discuss strategies to attack this disease in all of its forms at the genetic level.

DIABETES BUDGET

Mr. NATCHER. If you will now review for the committee briefly, Doctor, the current spending plans for diabetes throughout the department and for your specific Institute.

Dr. GORDEN. In fiscal year 1990, we will spend $150 million in diabetes-related research. The comparable NIH figure is $250,192,000.

In 1991 that translates to $157,007,000 for NIDDK and 261,192,000 for NIH at large.

Mr. NATCHER. The budget for diabetes is substantial, but it has remained essentially the same now for about two years, Doctor. Given the compelling needs for these funds, are you personally satisfied with this allocation?

Dr. GORDEN. Mr. Chairman, within our different components within the Institute, we are doing the very best we can to proportion our research dollars to every opportunity we have. We will continue to do whatever we can and use the very best judgment we can regarding how those resources are allocated among the different disease areas.

Mr. NATCHER. If you will, insert in the record at this point, Doctor, a copy of the most recent department-wide table on diabetes spending. If you will place that in the record for us, we would appreciate it.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

DIABETES AND RELATED RESEARCH

(Dollars in thousands)

	1988 Actual	1989 Actual	1990 Estimate	1991 Request
NCI.........	$819	$929	$960	$1,004
NHLBI.......	15,109	16,101	16,500	17,150
NIDR........	3,010	4,318	4,473	4,639
NIDDK.......	146,988	147,050	150,000	157,700
NINDS.......	7,995	9,383	9,682	10,107
NIAID.......	6,553	5,336	5,656	5,895
NIGMS.......	2,585	2,668	2,700	2,700
NICHD.......	12,168	13,343	14,000	14,600
NEI.........	22,050	21,086	21,405	22,548
NIEHS.......	178	196	203	211
NIA.........	4,772	4,805	4,973	5,170
NCRR.........	16,771	17,432	17,215	17,466
NCNR........	1,515	1,324	1,500	1,500
OD.........1/	369	753	925	502
TOTAL, NIH..	240,882	244,724	250,192	261,192

1/ Represents funding for RCMI which is now being funded within the NCRR.

KIDNEY DISEASES

Mr. **Natcher**. This subcommittee, as you know, has received letters from a number of members who are concerned about research in the area of different types of kidney disease. Now, describe to us, if you will, briefly the Institute's work in this area.

Dr. **Gorden**. We have a very comprehensive program that interfaces with all of our programmatic divisions. Diabetes is the most common cause of end-stage kidney disease. Thirty percent of all patients with total kidney failure who are entering into the HCFA Program have diabetes.

That means that kidney disease research cuts across all of the activities of our Institute, certainly in the diabetes program, into the nutrition program. Within the specific division directed at kidney and urologic diseases there are expenditures of approximately $95.5 million for 1990 in those programs alone.

Those programs encompass the whole panoply of other kidney diseases, including polycystic kidney disease, the inflammatory kidney diseases, the obstructive kidney diseases, the diseases of the lower urinary tract that lead to kidney failure, and efforts directed at trying to find the causes of and ways to prevent kidney failure.

That is the sort of fundamental thrust of the program in kidney diseases, a very comprehensive program which is programmatically directed from a single division, but encompasses all of our programmatic divisions, as well as our intramural program in Phoenix and in Bethesda.

Mr. **Natcher**. Can you give us a rough estimate of the portion of your budget which is directed at polycystic kidney disease in 1989, 1990 and what you propose for 1991?

Dr. **Gorden**. In polycystic kidney disease, figures are $1,600,000 in 1989; $1,700,000 in 1990, and $1,800,000 projected in 1991.

Mr. **Natcher**. Mr. Conte, I yield.

SENIOR BIOMEDICAL RESEARCH SERVICE

Mr. **Conte**. Thank you, Mr. Chairman.

Dr. Gorden, I join the Chairman, Chairman Natcher and the rest of the subcommittee in welcoming you back this year. You and your crew have done terrific work this past year.

I am confident that we can provide you with the tools necessary for your good work.

As you know, Dr. Raub, I introduced a bill to create the senior biomedical research service at NIH, and at ADAMHA. It is essential that we also pay the doctors and the scientists who work day in and day out to find the cures for all those deadly diseases what they truly deserve.

Dr. Raub, we have gone eight months now without a permanent director. Has compensation been one of the factors in discouraging the top candidates from throwing their stethoscopes into the ring?

Dr. **Raub**. Yes, sir, I believe that compensation has been a factor, not only the compensation for the position itself, but perhaps, even more importantly, the compensation for the array of senior scientists and science administrators who would be the agents through which the new director would achieve his or her goals.

Mr. **Conte**. Has it been difficult to retain senior scientists because of pay?

Dr. **Raub**. Yes, sir, it has. We have not been able to recruit a senior scientist into the intramural programs in 10 years. Over that same period of time we have had a 25 percent loss in terms of the numbers of scientists at senior positions. So, it is undoubtedly our single most important problem.

Mr. **Conte**. How about the physician's comparability allowance? How important is the PCA to your hiring efforts and doesn't it come up for renewal this year?

Dr. **Raub**. Yes, sir, the current authorities for the physician's comparability allowance lapse as of the 30th of September of this year. At present 291 of our physicians receive physician's comparability allowance.

As you know, we have the authority to provide up to $20,000 on an annual basis for a two-year contract, as determined by the individual's degree of training and experience and career achievements.

Of those 291 physicians, about 108 receive the full $20,000. The median is $17,000. It is an absolutely vital part of our recruitment and retention efforts.

Mr. **Conte**. Dr. Raub, you say that getting a competitive compensation package is probably the most important issue we have regarding the long-term health of NIH?

Dr. **Raub**. Yes, sir, there is no question about that. Our people are what make the organization go. Without the ability to retain the best and to attract the best, NIH inevitably will suffer.

TRAINING IN NEPHROLOGY RESEARCH

Mr. **Conte**. Dr. Gorden, as you know, much needs to be done to improve research in the field of pediatric nephrology. Your budget document states that efforts are being made to encourage more young doctors to enter careers in research. What specific efforts are being made by your Institute to attract young physicians to enter this field?

Dr. **Gorden**. We support research training in our intramural program, and we support it in a larger way through training grants and fellowships throughout the country.

In the nephrology area we have 28 such training grant programs in which there are from three to seven individuals on a training grant. These trainees are selected by the institution receiving the grant. Three of these training grants are specific to pediatric nephrology.

We also encourage all of these training grants to intermingle both adult nephrology and pediatrics. We feel that research training in pediatric nephrology and in other areas of nephrology have much in common.

We make a strong effort to encourage these programs to intermingle. We believe it will increase their strength. It is at the clinical level that they begin to diverge. That is, the clinical sub-speciality of pediatric nephrology is more different from adult nephrology than it is at the research interface. So our efforts have been not only to try to support those programs that have the real strength to create individual pediatric programs, but also to encourage those that don't to use the other nephrology resource training opportunities that exist to improve the base for pediatric nephrology as well.

Mr. CONTE. I understand that quite a few professional societies, including the American Society for Pediatric Nephrology, have recommended that NIDDK initiative is needed to stimulate and support basic and clinical research in pediatric kidney diseases.

What, in your professional judgment, needs to be done and, in your professional judgment, would expanding the current George O'Brien Centers to add centers specifically related to pediatrics be a valuable component of such an initiative?

Dr. GORDEN. Regarding the George O'Brien Centers, as you know, Mr. Conte, we have six such centers. They are nephrology and urology or nephrology-urology combined. We will have the next competition for those centers in fiscal year 1991 for funding in fiscal year 1992.

They were all begun at the same time in 1987 for a five-year program. In 1991, we will certainly encourage any pediatric group that would like to submit an application to do so. We would also encourage pediatric components of the George O'Brien Centers, but under our present operating procedures, we have tried very hard to maintain the fiscal independence of each of our center programs because of the difficulties that we have had in funding those programs over the years. It would be virtually impossible for us to expand those programs to create unique programs, such as pediatric nephrology, based on the budgetary considerations that we have at the moment. However, we will certainly do everything that we can to encourage pediatric nephrology programs to mount applications that will be competitive with the other programs that are out there at the moment.

Of course, in the broad aspect, pediatric nephrology would be very similar to the general difficulties that we are having in encouraging people to enter careers in biomedical science. Much of what you have discussed with Dr. Raub regarding recruitment and retention is a component of that same problem.

KIDNEY DISEASE OF DIABETES MELLITUS

Mr. CONTE. Dr. Gorden, I understand that an increasing number of patients with diabetic kidney disease are in the Medicare End-Stage Renal Disease Program. This has profound budgetary implications.

Mary Tyler Moore testified before us last year how important this research is. What progress is your Institute making in this critical area of research and how much is in the proposed budget for diabetic kidney research?

Dr. GORDEN. In fiscal 1987 we began an initiative to truly attack this really major problem. At that point we had just under $2 million in the research effort in that area. In fiscal year 1989 that amount had increased five-fold.

We have expanded into areas that address each of the major hypotheses in terms of how this disease process evolves and progresses. We have clinical trials. We have involved our intramural program. Our Phoenix intramural program study of the Pima Indians has a major role in this area. So, we have tried to at least cover all of the major bases, so to speak, in terms of the major thrust at the moment.

We think we have built this initiative at this point about as far as we can go in the immediate period. We are a little bit stretched out, so to speak, over a period of three years in terms of the rapidity of the growth of that program. In 1990 we will continue to try to allow that program to grow, but we will not be able to let it grow quite at the rate it has grown before.

Certainly kidney disease of diabetes mellitus is a major area of concern. It is one that we are going to continue to support in every way that we can.

COOLEY'S ANEMIA

Mr. **Conte**. Dr. Gorden, I understand your Institute has been involved in Cooley's anemia research for over 20 years now. You have been testing drugs which remove iron from the body, but as you know there has been difficulties from these drugs since they have to be injected. What efforts are being made to develop oral medication for Cooley's, and if these oral medications show promise, do you have funds to conduct further testing and how much will testing cost?

Dr. **Gorden**. What you say is quite true, Mr. Conte.

This is a very severe disease that affects primarily young people. It is a severe form of hemolytic anemia in which iron which has to be transfused into the body accumulates, and large amounts of iron become very toxic to the body.

There have been ways to inject materials called chelators, which accelerate the excretion of iron, but they have had to be given by needle. It has really been very difficult to implement this therapy in a successful way.

In the last year, four drugs have shown considerable promise as being effective as oral chelators in performing this same function. There is a fairly standardized FDA protocol which is required for these types of drugs. We have begun research in this area, testing two of these drugs and we would expand that research to include four drugs depending on how this goes.

We have funds to carry this through the initial phase, which will be approximately a million dollars. We have a cooperative effort with the National Heart, Lung and Blood Institute that will deal with another phase of it, but there is a third phase that would come into being in fiscal years 1991, 1992, and 1993, and which would cost something over a million dollars a year to continue this testing that the FDA requires—that is, official animal testing. They require a human test, and then they require a chronic testing in larger animals, and that becomes very, very expensive.

So we are prepared for the first part. The Heart Institute is prepared for their first part. We are quite prepared for what is going to happen in 1991 vis-a-vis testing. Depending on how many drugs eventually have to be tested, however, that may pose a major problem because, over three fiscal years, we would be looking at approximately $4 million, in that area. So we would have to report to you later where we stand and what the problem is going to be. We feel this is a very important thing. We feel that, for the first time, there is real promise in these drugs. Whether it will be one, two or all of them is hard to say at this point.

Mr. CONTE. One last question, my time is up. Dr. Gorden, gene replacement therapy has received considerable attention as a way to cure inherited disease like Cooley's. What are you doing in the area of gene replacement therapy?

Dr. GORDEN. Regarding Cooley's anemia, we have a considerable effort in genetics—not specifically gene replacement—but in areas that are referred to as gene switching. That is, there are different genes that control different forms of hemoglobin. It is produced in the fetus. It is produced in Cooley's anemia and produced in normal individuals.

There are manipulations that can cause the switching of one gene to the other, which is a very important research effort in this particular area. It is also important in sickle cell disease, which has a similar type of problem as Cooley's.

Gene therapy is something that is moving along at a very rapid pace, and which can apply to this disease and a number of others. We would hope that this will sort of come together, but it will be several years before that therapy has any possibility of really practical implementation.

Mr. CONTE. Thank you, Dr. Gorden. Thank you, Mr. Chairman.

Mr. NATCHER. Mr. Stokes, I yield.

DIABETES

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Gorden, in your formal statement you tell us that in four research areas the institute has made major contributions during the past 40 years. Diabetes is listed as one of those areas. You talk about the landmark advances in biotechnology, drug and device development, and clinical procedures.

In the area of diabetes is this statement true as it relates to minorities?

Dr. GORDEN. It is true in one sense, Mr. Stokes. It is true in the sense that there has been a general progress in this area that has affected these groups.

Unfortunately, many tribes in our Native American population have over four-fold the relative prevalence of diabetes. The Black population has at least one-and-a-half fold. The Hispanic population at least two-fold. We haven't done anything to change that. It is very unfortunate that the prevalence of diabetes is very high in these particular populations as well as in Native Hawaiians.

We don't know exactly why that is true, and we have a real effort at trying to understand why that is true so that we could attack it in a more systematic way. Trying to deal with each individual aspect of the disease is not going to be very productive. We have got to develop some central mechanism, some key factor that is relevant to all these different groups. That is really a major thrust of our effort now.

One of the really central programs that we have in studying this form of diabetes, which all of these groups have, is in Phoenix in our Pima Indian population. In that population we have some very important longitudinal studies that we think are going to be very relevant to all of our minority populations, and we are moving ahead as rapidly as possible in those areas.

Mr. STOKES. Well, when you say that you have these real efforts, tell us specifically what you are doing. We sit up here and we say over the last 40 years we have done all these great things. We have hit these landmarks in terms of this disease, and yet at the same time, admittedly, as it relates to minorities, we have done relatively little.

Now, obviously there is a reason for that, and I am trying to get at what we are doing to eliminate this type of disparity between whites and minorities in this country. So you tell me precisely what you are doing to try to accomplish this.

Dr. GORDEN. We are conducting studies which we are very hopeful are going to give us a much clearer picture of the earliest steps of the disease, and we believe that there is going to be a common denominator there among all the different groups we are talking about.

We believe that approach is going to be the most productive way to attack this disease in terms of treatment and cure. We have met recently with all of our minority groups. Dr. Sullivan chaired a conference for us in diabetes in the Black community. We have just met with our Native American community, and earlier we met with our Hispanic community. One of the things that we have come to realize is that attempting to deal with the issue with the available tools is extremely difficult and frustrating. This is particularly true for attacking obesity, which is one of the major features of this disease.

Most of what we have tried in the communities has not been very successful. We realized, as we talked to the groups, that we have a large number of different problems, each individual to the different groups, and that is why we are trying very hard to develop a more central kind of approach that would be applicable to all the groups rather than more diffuse types of approaches that would be relevant to each individual group.

We certainly have minority health issues as one of our primary considerations, and it is an effort that we are moving on as rapidly as we possibly can.

Mr. STOKES. Dr. Gorden, tell me how what you are telling me now is reflected in your budget. Tell us how much money is being targeted towards minorities and diabetes in your budget.

Dr. GORDEN. In our entire budget, we have approximately $28 million in programs that relate specifically to minority research programs within the Institute.

Mr. STOKES. How does that compare with the amount you have in the 1990 fiscal year budget?

Dr. GORDEN. That is the 1990 figure, and that is very similar to the figure we had in 1989.

Mr. STOKES. How much do you ask for in fiscal year 1991 for this purpose?

Dr. GORDEN. It will translate into a relatively similar figure.

Mr. STOKES. I don't know what you mean by relatively similar.

Dr. GORDEN. The amount targeted to this area is approximately $28,404,000 in 1989; $29,200,000 in 1990; and $30,400,000 in 1991.

Mr. **Stokes**. So your budget doesn't really reflect any real urgency in terms of our trying to get at this problem?

Dr. **Gorden**. I would prefer to think of it in a slightly different way, Mr. Stokes. That figure only relates to how we categorize projects that relate specifically to minority populations. I would like to think of it, as I say, as a more centralized effort in which the whole thrust of diabetes research is really being aimed predominantly at those individuals who are affected the most by the disease. And I would certainly feel and hope that the whole thrust of our diabetes budget of over $157 million would be viewed this way.

Mr. **Stokes**. Let me ask you this, Doctor. I understand your institute is studying the role of diet in kidney failure, which is a major public health problem. It is also a very serious problem among blacks and other minorities. What is the goal of your diet study?

Dr. **Gorden**. As you know, the numbers of patients with end-stage renal disease are increasing, and it is a huge amount of the HCFA budget. The study that you mention is referred to as the clinical trial on the Modification of Diet in Renal Disease (MDRD). It is testing the question of whether reductions in protein in the diet will delay or prevent end stage renal disease. This study, as you say, will have a special impact on those groups who have the highest prevalence of end stage renal disease, including Black Americans, and this study is well under way.

We expect to complete the recruitment by the end of this fiscal year. It then has two complete years to run. It runs from fiscal year 1991 to 1993. We feel that this is a major opportunity to find out whether this form of treatment is going to be useful for this particular problem.

It is a very important study. This year alone there have been two small studies reporting a positive result. We don't believe these small studies are adequate to answer the question, but they add to the impetus for our doing what we believe is a much more complete study.

Mr. **Stokes**. How much have you budgeted for this study?

Dr. **Gorden**. This study will cost in total $45,000,000 over the lifetime of the study. It will cost in fiscal year 1990 $7,000,000. In fiscal year 1991 and in 1992 it will cost $10 million and $10.5 million respectively.

Mr. **Stokes**. Thank you, Dr. Gorden. Thank you, Mr. Chairman.

Mr. **Natcher**. Mr. Early, I yield.

CYSTIC FIBROSIS

Mr. **Early**. Dr. Gorden, the chart you showed about cystic fibrosis is interesting. I am going to be specific with you in regards to cystic fibrosis because I have generalized with other directors on something that bothered me. You showed me a chart that showed 1953, and that in 1989, 36 years later, you have identified the gene; is that correct?

Dr. **Gorden**. Yes.

Mr. **Early**. That is a long time, Doctor.

Dr. **Gorden**. Yes, sir.

Mr. **Early**. Now we get there after 30 years, and I don't know how many people died of cystic fibrosis over this crisis, over this time. In your statement you say, "Finally, in 1989 a team of NIDDK supported American and Canadian scientists reported how they had walked and jumped up and down the chromosome to pinpoint the gene in an approach called reverse genetics."

Do you say that in your statement, Doctor?

Dr. **Gorden**. Yes, sir.

Mr. **Early**. "Now armed with the CF gene, researchers can design membrane study systems to find ways to make the defective protein work correctly and ultimately to seek ways to correct the genetic defect in CF patients through gene therapy. Will those studies be done with grants?

Dr. **Gorden**. Yes, sir, predominantly.

Mr. **Early**. Fine. Are we going to wait another 36 years, Doctor?

Dr. **Gorden**. I certainly don't think so.

Mr. **Early**. Well, Doctor, are you going to downward negotiate those grants?

Dr. **Gorden**. Well——

Mr. **Early**. Doctor, that is a specific question. Are you going to exclude those grants from downward negotiation?

Dr. **Gorden**. No, sir.

Mr. **Early**. So you are going to downward negotiate those?

Dr. **Gorden**. Yes, sir.

RESEARCH CENTERS

Mr. **Early**. You told us a couple years ago, how many cystic fibrosis centers do you have, Doctor?

Dr. **Gorden**. We have five.

Mr. **Early**. All right. Last year you said you would have four and you would fund them in 1990 at $3,800,000. In your 1991 request, you don't seek any new money for your centers, Doctor.

You are coming in, for all the centers, 40 centers, at $33,700,000, is that the number?

Dr. **Gorden**. Yes, sir.

Mr. **Early**. Doctor, will there be downward negotiation for new and competing grants with this budget request?

Dr. **Gorden**. Yes, sir.

Mr. **Early**. New and competing grants are well below the past levels, and for the fourth year in a row you have downward negotiations beyond the problem or crisis point, Doctor?

Dr. **Gorden**. Certainly, it is a very large amount.

Mr. **Early**. Doctor, all the other directors have told us for the last four years that 10 percent was the crisis point. Is that right, Doctor?

Dr. **Gorden**. Yes, sir, we said that.

Mr. **Early**. Doctor, you plan to fund 40 research centers in 1991, the same number as 1990, at the same level, $33,700,000. This is less than the amount expended in 1989 to fund the 40 centers, isn't it, Doctor?

Dr. **Gorden**. Yes, sir.

Mr. **Early**. How can you be telling us, Doctor, as far as that—we have got a major discovery in 1989 on the CF gene. If I had CF or any of my kids had it—this is a disgrace, Doctor, what we are not going to do. Let's go to your specific centers, Doctor.

These numbers can't be accurate, Doctor. Your research centers didn't downward negotiate 21 percent in 1989, did they, Doctor?

Dr. **Gorden**. Yes, sir.

Mr. **Early**. Downward negotiate. They didn't downward negotiate 25 percent in 1990, Doctor?

Dr. **Gorden**. Yes, sir.

Mr. **Early**. Do you estimate, in this as farce of a budget that we have, that you are going to downward negotiate in cystic fibrosis centers by 30 percent?

Dr. **Gorden**. Yes, sir.

Mr. **Early**. How can this happen, Doctor? How are we leveling with anybody? How can this administration, you and the NIH or this Congress let that happen when you're telling people with cystic fibrosis that we are on the verge of some breakthroughs?

Dr. **Gorden**. It is a very difficult situation.

Mr. **Early**. It is an embarrassing situation, isn't it, Doctor?

Dr. **Gorden**. Yes, sir.

Mr. **Early**. How can OMB—we had a discussion yesterday about mammograms, testing, and we said it is no good if you don't have people that know how to read the mammogram. How can OMB tell you what to do with cystic fibrosis? How can they tell you to cut 30 percent, Doctor, and you are going to be the director of this Institute and suggest to the American people we are trying to solve the problem of cystic fibrosis?

Dr. **Gorden**. It is a difficult dilemma for us, Mr. Early.

Mr. **Early**. Are we going to wait—would we have to wait another 37 years, Doctor, if you had more money for cystic fibrosis, and we don't ever tell you what diseases—if you had more money so that you wouldn't have to downward negotiate your grants by outrageous levels, your centers by outrageous amounts? Would you get there faster?

Dr. **Gorden**. I think that——

Mr. **Early**. It is a specific question, Doctor. Would you get there faster?

Dr. **Gorden**. Yes, sir, I think we would.

CYSTIC FIBROSIS

Mr. **Early**. I don't know what we are doing here, Doctor. You know, my opinion is the same as most of the committee. Progress on cystic fibrosis has taken so long. You showed us a map of 36 years, and we don't know how many more.

If I have cystic fibrosis, what do I care if you discovered the gene if the condition isn't going to be treated. All I want to do is read about what you are doing as far as progress?

We are going in the front door with these institutes, keeping them open to establish a bureaucracy, and no progress is coming out the back door because there is not enough money. Doctor, is anyone else in the private sector doing anything with this?

Dr. **Gorden**. Yes, sir, there are some very important efforts in the private sector, the Howard Hughes Medical Institute has made important contributions, the Cystic Fibrosis Foundation has made important contributions, but I think that the bulk of the contributions have come from the NIH.

Mr. **Early**. But we have waited 36–37 years just to get where we are. Have those foundations been doing anything in that time?

Dr. **Gorden**. Yes, sir. Not the Howard Hughes Foundation. It has only really been in existence a short time.

Mr. **Early**. Who has been doing research since 1953 in cystic fibrosis?

Dr. **Gorden**. Predominantly the NIH institutes and the Cystic Fibrosis Foundation, but to a much smaller extent.

Mr. **Early**. I think the Cystic Fibrosis Foundation went out and raised several million dollars for research, didn't they, Doctor?

Dr. **Gorden**. Yes, they did. They have made some very important contributions, but in comparison, the NIH has been by far and away the largest contributor to this important problem.

Mr. **Early**. Doctor, how many specific grants have you made in the last couple years for cystic fibrosis research?

Phase supply that for the record.

[The information follows:]

NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES—CYSTIC FIBROSIS PROJECTS

	1987	1988	1989
Regular research project grants	33	38	34
Research centers	1	2	5
Research career awards	1	1	
Intramural research projects	3	5	5

DOWNWARD NEGOTIATION OF GRANTS

Mr. **Early**. Have they all been downward negotiated?

Dr. **Gorden**. Yes.

Mr. **Early**. Basically how much money does a grantee get?

Dr. **Gorden**. The average grant size cost in fiscal year 1991 is estimated to be $195,000.

Mr. **Early**. With your downward negotiation, giving them $195,000, then you are going to cut them drastically—12 percent last year and 11 percent this year?

Dr. **Gorden**. Yes, sir.

Mr. **Early**. And we are going to say we are doing something?

Dr. **Gorden**. You are quite right, Mr. Early.

It is a very difficult problem for us. The dilemma obviously for us is whether we have fewer grants or more downward negotiation. And, quite honestly, I think we have an important obligation to try to maintain the morale of science, too. There is no other organization that is large enough except the NIH to do that. We have to make decisions that we believe are going to be in the interest of research and the interest of the morale of research. When we get in the dilemma of how many grants we can support or how much we are going to negotiate, those decisions can't always be the same.

I think any time we make one decision we have to try to make the best one we can make at that particular time.

Mr. **Early**. Doctor, they are not made in the interest of research. They are made in the interest of OMB, finances. The Defense Department doesn't do that, the Department of Energy doesn't do that. They have got that new super collider which is estimated to have a $2,000,000,000 overrun. The fact is that it is new and exciting and it is in the paper, while your people and cystic fibrosis research have been in there for 40 years, you are not exciting, you are not sexy.

This is terrible, Doctor, what we are not doing.

Dr. **Gorden**. Yes, sir.

Mr. **Early**. I want to ask questions, not lecture, but, my goodness, this is discouraging, Doctor. You know what will happen if some member of the President's staff or some member of this Congress gets cystic fibrosis? Then we will treat it. What a disgrace to the American public.

LIVER TRANSPLANTS

Mr. **Early**. Doctor, I want to shift to your statement with regard to liver transplants. On liver transplants, and I have a specific interest in this, you say that a doctor in Pittsburgh is the leading researcher, Dr. Thomas Starzl.

Dr. **Gorden**. Yes, sir.

Mr. **Earl**. I understand that of all the liver transplants, 50 percent of them are done in Pittsburgh, is that right?

Dr. **Gorden**.The NIDDK supports a Liver Transplantation Database. The Coordinating Center of the database reports that in 1988, 1,710 liver transplants were performed in the United States. Of that number, 505, or 29.5 percent, were performed on both adults and children at two centers in Pittsburgh.

Mr. **Early**. These numbers that are in your statement aren't very exciting about the liver transplants. I have a specific constituent who has been waiting for a liver transplant for several months now.

This system just isn't going too well. Health research is no longer exciting. It is no longer on the front burner for anybody, I guess.

Dr. **Gorden**. Liver transplantation depends upon organ procurement, as you say, which is a major problem.

One of the major advances in the last two years has been a new solution that allows for much longer preservation of an organ from the time it's collected to the time it's transplanted, and that opens up a much greater opportunity to obtain organs.

This is only something that has happened within the last two years, and I hope that it is going to expand the donor pool. It will certainly be one important aspect.

There have been several other new things. There have been mechanisms to actually split livers, so that you can have more transplants from a single liver.

Mr. **Early**. Doctor, we cannot get the organs. What bothers me is, and I don't want to be morbid about this, but we invaded Panama, and there were a lot of deaths, and I don't think we obtained any organs.

I mean, I would think if we had the network that we would be doing all these things. And you know, my gosh, health research should get back to being the prestigious group it used to be.

I mean, we are not doing anything because of these problems, not just salaries.

Doctor, then there's another problem; if we straighten out the centers, if you don't downward negotiate the centers then you will have to take it off the grants; won't you?

Dr. GORDON. Yes, sir.

Mr. CONTE. I have a lot of other questions, Mr. Chairman; I will submit them for the record.

Mr. WILLIAMS. Mr. Early, if I could just go back and interrupt, I would like to clarify one point that you made earlier in your exchange, if that is okay.

In your discussion on research centers, you talked about the role of OMB and the establishment of the amount of money for that activity.

I think what is fair to say is that the Department is in discussions with the Office of Management and Budget in regard to the amount of money for the National Institutes of Health as a total activity.

In support of that, decisions are made within the National Institutes of Health and elsewhere in the Department about how that money ought to be allocated. The research centers themselves are not dictated by the Office of Management and Budget; that line is the result of more global negotiations and more global decisions.

Mr. EARLY. Mr. Chairman, may I respond to that?

Mr. NATCHER. Go right ahead.

Mr. EARLY. Even with that, my problem is with the whole process as far as OMB tells them what to do because you tell them how much money they've got and they have to back into the amount of money. They don't drive forward into anything. They back into everything, and I think that is your business; okay?

My criticism isn't with you. My criticism is with them, and if the cystic fibrosis people have barged in your door, you tell them how much money they have got.

Mr. WILLIAMS. But the process allows quite openly for the National Institutes of Health to let everyone know what their needs are and what kind of resources they could use at any given time.

Now, the trade-offs are made in the budget process as to what is manageable within the resources available.

Mr. EARLY. What was your original——

Mr. WILLIAMS. But the National Institutes of Health has the opportunity and aggressively pursues the opportunity to let people know what its needs are.

Mr. EARLY. Dr. Gorden, what was your original request?

Dr. GORDEN. Our original request to the NIH?

Mr. EARLY. In its initial stage.

Dr. GORDEN. Our initial request was $808,391,000.

Mr. EARLY. And how much is your budget now?

Dr. GORDEN. $605,349,000.

Mr. WILLIAMS. I am not saying it's fair to debate whether the budget is adequate or not, that it's lower now than it was when the various Institutes prepared their budgets is very obvious.

I just want to make the point that the Institutes have the opportunity to say what their needs are, and that those needs are taken into account in budget decisions. But there is a finite amount of resources, and the President ultimately decides, at least for the Executive Branch, how those resources will be allocated.

Mr. Early. And he decided that defense is more important than cystic fibrosis and all the other diseases. That is my point.

Thank you, Mr. Chairman.

Mr. Natcher. Dr. Gorden, we want to thank you and your associates for appearing before our committee at this time on behalf of your budget request for the fiscal year 1991.

Dr. Gorden, it's been a good hearing, and we appreciate it.

Dr. Gorden. Thank you, Mr. Chairman.

Mr. Conte. Mr. Chairman, I didn't realize we were going to quit now. I have about 50 more questions. I will submit them in the record, and you can answer them, as if I had asked them.

Dr. Gorden. Yes, sir, I'll be happy to do that.

Mr. Natcher. Yes. Thank you very much.

[The following questions were submitted to be answered for the record and the justifications follow:]

NUMBER OF GRANT APPLICATIONS

Mr. Natcher. Doctor, as you know, the number of grant applications submitted to the NIH as a whole has increased dramatically during the last ten years. The situation with your Institute is a bit confusing because of the Arthritis Institute, but it appears that the number of applications has not grown in the last five years. What accounts for this situation?

Dr. Gorden. We believe that the steady decline in the awards rate or our ability to fund new and competing research grants has discouraged many potential investigators from applying for research grants in our program areas.

DIET AND RENAL DISEASE TRIAL

Mr. Natcher. What is the total cost of the Diet and Renal Disease Trial in 1991 and to completion?

Dr. Gorden. The cost of this clinical trial will be $10.4 million in 1991 with a projected total cost through completion in 1992 or 1993 of $45 to $50 million.

Mr. Natcher. We understand that there have been problems in recruiting volunteers for this study. Has this been resolved?

Dr. Gorden. Typical of many clinical trials, the recruitment of study participants was less than expected in the beginning. This reflected the time required to generate publicity about the study. However, study investigators have had ready access to mass media nationwide, including television, radio and newspapers to solicit volunteers, for the study and recruitment is nearly at target goals. For example, earlier this year an article about the study appeared in USA Today and resulted in 500 telephone calls to the National Kidney and Urologic Diseases Information Clearinghouse for more information about the study. With this response from the public as well as referral of study participants by practicing physicians, the Modification of Diet in Renal Disease Study investigators are confident that they will attain their recruitment goals by the end of this year.

INTERSTITIAL CYSTITIS

Mr. Natcher. The budget documents indicate that you have expanded your work in the area of IC (interstitial cystitis). Could you tell us how many new grants are expected in this area in 1990 and 1991, and also tell us about the center program?

Dr. Gorden. I am pleased to report that we are making progress toward our goal of building a high quality base of research related to interstitial cystitis, a painful and often debilitating bladder disease of unknown cause. In 1986, we had virtually no research in this area. Today, however, largely due to the efforts and encouragement of the Institute staff, urology researchers, and the Interstitial Cystitis Association, we are supporting 10 basic and clinical research grants related to IC, as well as a pilot database on IC, for a total of approximately $1.8 million in FY 1990. We believe this growth represents a significant and promising program expansion. We will be issuing another Program Announcement in Fiscal Year 1990 to encourage additional research grant applications in IC. We welcome research grant applications in this important area and hope to be able to fund additional scientifically meritorious applications in FY 1991 as a result of this solicitation.

With respect to centers, we recently made a supplemental grant award to an existing George O'Brien Kidney and Urologic Diseases Center at Northwestern University Medical School for the establishment of an IC pilot database. We are very hopeful that this new effort will give us important research clues to IC, as well as provide a source of well-defined patients for possible future clinical trials on IC.

Mr. Natcher. The IC groups have suggested that this Committee direct you to establish a patient registry. Is this a good idea at this time?

Dr. Gorden. The NIDDK has carefully considered the possibility of establishing a national registry on IC. The Institute has concluded, however, that it would be most appropriate to test the usefulness of the newly developed diagnostic criteria for IC before pursuing the concept of a national IC registry.

In its five-year plan for IC submitted to the Congress in April 1989, the Institute outlined the advantages of establishing a pilot IC data base, rather than a national registry, at this point in time. The most important consideration is that IC remains a disease of widely varying symptoms. Thus, for research purposes, it is important to begin to determine whether the new diagnostic criteria are actually useful in defining patients who share similar characteristics. These diagnostic criteria are only in their "test phase" at this point. They are based on the preliminary set of diagnostic criteria which the NIDDK has developed in conjunction with the IC research and IC voluntary health communities.

We believe that such a pilot data base offers the most promising opportunities for establishing the criteria on which to make a definite diagnosis of the presence or absence of IC in a well-defined group of patients with these symptoms and signs. It also provides a well-defined group of patients for possible future clinical studies and trials. Given the current state of knowledge about IC, the NIDDK believes that it would be scientifically premature, at this time, to establish a national registry for IC patients, for whom clinical data could be expected to be extremely variable and difficult to interpret.

In FY 1989, the NIDDK made a grant award to an existing George O'Brien Kidney and Urologic Diseases Research Center to establish a pilot IC data base. We are very hopeful that the data collected and analyzed through this new effort on a well-defined subpopulation of IC patients will provide a solid foundation on which we can then begin further clinical and basic explorations of underlying causes of IC and some ideas for possible therapeutic interventions.

RESEARCH TRAINING

Mr. Natcher. The Committee has been approached over the years by a number of groups who are concerned about training opportunities for their specialty. You added 60 training slots in 1990. How have these been allocated?

Dr. Gorden. First, I must emphasize that our programs are restricted to training future research investigators, not practicing specialists. Second, we have not allocated the additional slots for either 1990 or 1991 to specific disease areas. We will depend primarily on the peer review process to identify the most promising applicants, but funding decisions will also consider the need to bolster areas where the research programs need strengthening.

PURINE DRUG THERAPY

Mr. Conte. I hear that purines hold great promise for certain types of drug therapy. Can you tell us more? How would purine therapy work?

Dr. Gorden. Most of the effects of purines such as adenosine and its analogs are mediated through specific membrane receptors called purinergic receptors. In most tissues these receptors are coupled to inhibition of the enzyme adenylate cyclase, although some receptors mediate adenylate cyclase activation. In particular, adenosine and its analogs regulate a component of adenylate cyclase called G proteins. The adenylate cyclase system is a major mechanism of signal transmission and cellular regulation, and agents which effect this system have the potential for very potent and diverse effects. NIDDK supports a significant body of research on adenylate cyclase and the G proteins.

Mr. Conte. What diseases might be treated by this new line of drugs?

Dr. Gorden. The potent effects of the purine adenosine on heart rate and blood pressure have been recognized for over fifty years. The more recent recognition of its effects on cardiac contractility and electrophysiology led to development of drugs for use in cardiac arrhythmias and heart failure. Adenosine has effects on renal blood flow and renin release, gastric acid secretion, fat cell metabolism, platelet aggregation and lymphocyte function. In fact, most organ systems in the body are regulated in part by the local release of adenosine, so there is a wide variety of potential therapeutic applications of these agents.

ULCERS

Mr. Conte. Dr. Gorden, can you tell us a little bit about the bacteria story regarding how ulcers are caused. These ulcers seem to keep coming back like an old penny. Is there a treatment available that will keep this from happening?

Dr. Gorden. In recent years, evidence of a spiral organism called Helicobacter pylori has been reported on the mucous membrane of the gut in patients who have gastritis or peptic ulcer disease. Research has shown that this organism is pivotal to the origin and development of these conditions, and, therefore, has broad implications for both diagnosis and therapy. When an imbalance exists between the acid secreted by the stomach and the body's resistance to that acidic activity, peptic ulcer disease is the result. NIDDK researchers have found that the bacterium causes a progressive inflammation from the cavity to the body of the stomach that leads to gastritis. Once these cells are damaged, they are susceptible to acid and peptic digestion and the formation of ulcers. In addition to mapping the pattern of gastric activity, NIDDK grantees have devised methods for detecting the bacterium, and most significantly have demonstrated that ulcers can be healed and their recurrence prevented. Using a combined therapy of bismuth and antibiotic therapy, the bacterial organism can be eradicated. These research results are encouraging and may ultimately lead to wide-scale control of peptic ulcer disease.

PCR TECHNIQUE

Mr. Conte. Doctor, I have been hearing so much on how the PCR technique has revolutionized biomedical research. Can you tell us how PCR is being used at your institute and what areas are of particular promise?

Dr. Gorden. You are quite right, Mr. Conte. Biomedical research has already benefited greatly from our ability to amplify very small portions of DNA--in some cases only trace amounts--using PCR, the polymerase chain reaction. A major use for PCR is in studying genetic metabolic disorders, an area of research that is part of the mission of our Institute. Many NIDDK grantees are using PCR in basic research and to study diseases such as Lesch-Nyhan syndrome, Fabry disease, and maple syrup urine disease. In addition, an NIDDK grantee recently developed a new detection method for genetic mutations which couples PCR with a technique called competitive oligonucleotide priming. The combination of these techniques provides a powerful yet simple general strategy for the detection of single DNA base differences.

Most notable during the past year, however, was the discovery of the cystic fibrosis gene by NIDDK grantees. The application of PCR was integral to, and in fact hastened, this landmark research. One of the investigators called PCR a "dream method" for diagnosing inherited diseases. While PCR is not foolproof, we believe it holds tremendous value in both research and clinical applications.

NEW IMMUNOSUPPRESSIVE DRUG

Mr. Conte. Doctor, I understand that a new drug, FK-506, has been developed that is most promising in reducing rejection rates in organ transplants. What are the clinical implications of this drug?

Dr. Gorden. FK-506 is a medication that was developed by the Fujisawa Pharmaceutical Company in Japan about five years ago. This company was looking for new drugs that suppress the immune system. FK-506 was then extensively investigated by NIDDK grantee, Dr. Thomas Starzl, and his co-workers at the University of Pittsburgh. They showed that FK-506 was 100 times more potent than cyclosporin [the immunosuppressive medication that is currently used in transplantation] and that FK-506 prevented rejection in several animal models, including rats, dogs and baboons. Based upon their promising animal experiments, Dr. Starzl obtained permission to use FK-506 in humans in March 1989. The early results were startling. The Pittsburgh group found that they could reverse severe organ rejection after failure of all other medications [prednisone, cyclosporin, imuran and OKT3]. Furthermore, FK-506 could be used as a single agent to prevent rejection and was safer and better tolerated than cyclosporin and prednisone. Dr. Starzl has worked closely with the Fujisawa Company and the Food and Drug Administration (FDA) to put FK-506 on the "fast track" for possible licensure by the FDA for use in organ transplantation. A controlled trial of FK-506 has begun in Pittsburgh and a large, multicenter controlled trial comparing FK-506 to cyclosporin for liver transplantation is now being designed in collaboration between NIDDK and three large transplantation centers.

It should also be pointed out that FK-506 may have important uses outside of organ transplantation. In particular, FK-506 may be an ideal drug to treat the so-called "autoimmune" diseases, such as Type I diabetes, rheumatoid arthritis, lupus erythematosis, ulcerative colitis, Crohn's disease, primary biliary cirrhosis and sclerosing cholangitis (to name just a few). The possible role of FK-506 in treating autoimmune diseases is very exciting and has led NIDDK staff to begin discussions and collaborations with the Fujisawa Company, the Food and Drug Administration, Dr. Starzl and our grantees to set up trials of this agent in these important diseases.

Mr. Conte. In the long-run do you think it will reduce the cost associated with organ transplantation and its complications?

Dr. Gorden. If FK-506 is as effective and safe as it has appeared in Dr. Starzl's initial study, it may well replace cyclosporin as a primary means of prevention of rejection, not just in liver transplantation but also in kidney, bone marrow and heart transplantation. Because FK-506 seems to be more potent and safer than cyclosporin, it may well improve survival as well as reduce the cost of liver transplantation. A safer immunosuppressive medication will certainly make the management of the myriad of complications that come with transplantation easier. Because FK-506 may obviate the need to use prednisone and does not have the kidney and neurologic side effects of cyclosporin, it may improve the quality of life of the patient with an organ transplant.

Mr. Conte. What other anti-rejection drugs show promise?

Dr. Gorden. Besides FK-506 there are no other anti-rejection drugs that show promise and are near to use in humans. The monoclonal antibody against T cells known as OKT3 has been shown to be very valuable in reversing acute rejection. The major problem with OKT3 is that it is a mouse monoclonal antibody. Attempts are being made to prepare human monoclonal antibodies to T cells which would be better tolerated and safer.

POLYCYSTIC KIDNEY DISEASE

Mr. Conte. Doctor, Polycystic Kidney disease affects more than 500,000 Americans. It's the third leading cause of renal failure in the U.S. What avenue of research is currently being done in this field?

Dr. Gorden. Adult Polycystic Kidney Disease (PKD) is associated with a genetic defect, which has been linked to a specific chromosomal site within families. Investigators now are trying to identify the specific defect.

In addition, this disease is associated with the presence of kidney cysts, hypertension, and rupture of blood vessels in the head. Therefore, investigators are also studying these complications in patients and animal models, as well as conducting studies at the cellular and molecular level.

A number of important questions remain unanswered and the new leads provided by the studies mentioned above emphasize the need to expand the research base in the study of PKD.

Mr. Conte. What are the priority areas of research in polycystic kidney disease?

Dr. Gorden. Polycystic Kidney Disease is an autosomal dominant inherited disorder. Therefore, it is passed from affected parents to children so that each offspring has a 50% chance of inheriting the gene. Given the sophisticated research technology currently available and the major programs recently made in this area, a better understanding of the mechanisms leading to the formation of kidney cysts, which lead to end-stage renal disease, should be possible in the future.

In addition, it should be possible to identify the genetic defect and also to control the complications of PKD that occur outside of the kidney.

The priority areas of research are: isolate and identify the gene defect; develop techniques that affect the regulation of the gene or the means to replace the defective gene; identify factor(s) that promote cyst growth; continue the study of experimental models of PKD utilizing state-of-the-art research tools at the in vitro as well as in vivo levels; continue studies of the natural history of PKD; and develop and test possible therapeutic interventions aimed at limiting or preventing progress of the disease processes.

HEPATITIS C

Mr. Conte. I am pleased to learn that your Institute is taking a major role in finding ways to treat the newly discovered hepatitis C. That alpha interferon shows great promise in the treatment of this disease. How does this drug work against the hepatitis C virus?

Dr. Gorden. Alpha interferon has recently been shown to improve the liver disease of chronic hepatitis C. The initial studies were done at the NIH Clinical Center and this last year a large, multicenter United States trial has confirmed the beneficial effects of alpha interferon therapy in chronic hepatitis C. The medication seems to work by inhibiting the hepatitis C virus, lowering the level of infection and thereby, making the disease milder. Investigations are now underway attempting to identify the optimal doses of interferon and how long patients should be treated. Low doses of interferon given for a short period (four to six months) are not as effective as higher doses given for longer periods (one to two years). Major work is also underway in developing direct tests to measure the hepatitis C virus, so that physicians can monitor treatment and will be able to decide when the medication has effectively eradicated the virus infection. At the NIH Clinical Center, NIDDK investigators are actively searching for other agents that might be effective in this disease.

Mr. Conte. How many people are infected with hepatitis C?

Dr. Gorden. Hepatitis C, or what used to be called non-A, non-B hepatitis, is a common form of viral hepatitis in the United States. It can cause acute hepatitis as well as chronic hepatitis. Acute hepatitis C accounts for about 30 percent of all cases of acute viral hepatitis as estimated by the CDC. The prevalence of chronic hepatitis C is more difficult to assess, but using the recently developed tests for hepatitis C, it is estimated that one to two percent of Americans, or about two to five million people, have chronic hepatitis C infection. It is important to remember, however, that only 10-15 percent (about 500,000) of these people with chronic hepatitis C infection have chronic liver disease, the rest are "healthy" carriers. These healthy carriers of hepatitis C do not suffer from the disease themselves, but they can spread it to others by blood donation or accidental exposure of someone else to their blood or secretions.

Mr. Conte. Can alpha interferon work against other agents as well?

Dr. Gorden. Alpha interferon is a host protein that is made in response to virus infections and has anti-viral action against almost all viruses. For this reason, alpha interferon is being evaluated in many chronic viral infections, including the acquired immunodeficiency syndrome, chronic delta hepatitis and human papillomavirus infections which cause genital warts.

RDA ALLOWANCES

Mr. Conte. Dr. Gorden, I was pleased to see that a new edition of the Recommended Dietary Allowances was published recently. Tell us about your Institute's contributions to this effort and the importance of this guide.

Dr. Gorden. NIDDK has supported the development of the Recommended Dietary Allowances (RDAs) for more than 25 years, and most recently supported the publication of the tenth edition under contract. At the Federal government's request, the National Research Council of the National Academy of Sciences has carried out periodic reviews of the essential vitamins and minerals in the diet, the results of which are published in the form of guidelines or RDAs. By providing a standard against which adequate nutrient intake or nutrient deficiencies can be measured, the RDAs meet a critical need in the conduct of nutrition research. Over the years, the use of this guide has been extended by various groups to provide nutritional guidance for healthy persons, and for the development of nutrition programs and policies. For example, the U.S. Department of Agriculture uses the RDAs to evaluate the adequacy of the U.S. food supply, to establish food standards for food assistance programs, and to determine the nutritional status of the U.S. population. It was from the seventh edition of the RDAs that the Food and Drug Administration derived its U.S. Recommended Daily Allowances, which set the standards that guide how the nutritional content of foods is listed on product labels. One more use of the guidelines is to assist in the development of new food products.

DIGESTIVE DISEASES CENTERS

Mr. Conte. How many digestive disease centers will you support in FY 1991?

Dr. Gorden. We expect to continue to support 12 digestive disease centers in 1991.

Mr. Conte. How close will their funding be to the level recommended by peer reviewers?

Dr. Gorden. We will have to reduce the recommended levels of support by about 30 percent. The other option we are beginning to consider is to cut back the number of centers so that the remainder can be more adequately supported.

DIGESTIVE DISEASES ADVISORY BOARD

Mr. Conte. Doctor, the Digestive Diseases Advisory Board has recommended several clinical trials, and your Institute has prepared a report to the Congress commenting on these recommendations. Can you tell us which trials the Institute believes are the most promising and what they would cost?

Dr. Gorden. As requested by the Committee on Appropriations for the FY 1990 budget, the NIDDK reviewed the recommendations of the National Digestive Diseases Advisory Board for clinical trials in digestive diseases and considers the following trials to be particularly worthy of pursuit: A clinical study of gallstone recurrence following extracorporeal shock-wave lithotripsy; clinical trials in the treatment of primary biliary cirrhosis; immunosuppressants in Crohn's disease; and the role of Helicobacter pylori in peptic ulcers. First year costs for these clinical trials are estimated at $7.5 million and total costs at $36.5 million.

DIABETES CONTROL

Mr. Conte. What is known about whether tight control is better at preventing the complications of diabetes versus loose control?

Dr. Gorden. The origin of the long-term complications of diabetes continues to be one of the major controversies in diabetes mellitus. Although it is well-established that genetic predisposition as well as long-term elevated blood sugar (hyperglycemia) are both involved in the pathogenesis of complications, the exact role of each of these two factors is far from being defined. Several studies have suggested that chronic hyperglycemia is a major factor in the development of complications. However, all of these studies have suffered from several weaknesses including small sample size, short duration, marginally significant results and little or no precise measurement of potential risks of tight control. In fact, several studies have observed the perplexing phenomena of a temporary worsening of diabetic eye disease following the institution of a tight control regimen, while other studies have reported some improvement in indicators of renal function. Such observations, therefore, preclude a definitive conclusion of a beneficial effect of intensive insulin therapy.

Mr. Conte. Can you tell us more about the clinical trial that you are sponsoring which looks at this very question?

Dr. Gorden. The Diabetes Control and Complications Trial (DCCT) is a large multicenter, randomized, clinical trial designed to answer two questions. First, will intensive treatment prevent the development of early complications in those without any and, second, will intensive treatment halt the progression of early complications in those with the earliest signs of complications? The DCCT is the only study in the world that is addressing the first of these questions; all others have focused only on the second issue. Recruitment of 1,441 subjects needed for the trial has been completed. The earliest recruited subjects are now completing their sixth year of follow-up and the most recently recruited subjects are completing their first year. It is expected that the study will be finished in 1993 and results reported in early 1994. Adherence to the study among the patient volunteers has been outstanding. In all respects, the trial is meeting or exceeding expectations.

Although answers to the central questions posed by the DCCT will not be available for several years, the DCCT is already generating scientific and medical information with immediate impact on the diabetes community. For instance, neurologic evaluation of the first 300 volunteers for the trial disclosed that approximately 40 percent already had clinical nerve damage, which significantly correlated with age, duration of diabetes, and male gender. A DCCT study of two techniques to evaluate diabetic eye disease disclosed that the two are equally effective. However, one (fundus photography) is noninvasive, less risky and less costly, making it the preferred technique for this assessment. Most importantly, the trial has demonstrated that while it is possible to achieve lower blood glucose levels with intensive treatment, it is associated with more episodes of severe hypoglycemia (low blood sugar) and with weight gain. Thus far, 23 scientific publications have resulted from the DCCT with many additional contributions to the understanding of diabetes expected for many years into the future. At the present time, the DCCT Study Group is exploring the feasibility of incorporating an investigation into the genetics of the complications of diabetes utilizing the families of the 1,441 DCCT participants, thus providing a unique opportunity to unravel the relative roles of genes versus one's metabolic environment in the pathogenesis of diabetic complications.

LIVER TRANSPLANTATION

Mr. Conte. You mentioned the quantum leaps we've seen in the area of liver transplantation. Primary biliary cirrhosis is now the number one cause of liver transplantation. Can you tell us more about this disease and what research is being done on it?

Dr. Gorden. Primary biliary cirrhosis (PBC) is an uncommon autoimmune liver disease that is marked by a gradual inflammatory destruction of the small bile ducts of the liver. Its cause is unknown, and there are no known beneficial therapies. The disease leads to progressive liver injury that results in scarring and death from liver disease within two to ten years of the onset of symptoms. As a consequence, PBC is the single most common indication for liver transplantation in adults, with an estimated 200 patients undergoing the procedure each year.

In an attempt to offer some remedy to the dismal prognosis of this disease, the NIDDK has supported several randomized trials with small numbers of patients. Encouraging results of these studies reported positive effects of no less than five therapeutic agents on liver function tests, mortality, and histology. These pilot trials should provide an impetus to further evaluate these therapies, either alone or in combination. Only in this way can we identify the most optimal treatment to manage the natural long-term course of PBC and ultimately halt progression of the disease. Another recent research advance has resulted in development of sensitive diagnostic assays for the detection of PBC. These findings will aid further investigations and help to more readily uncover the mechanism that causes the disease. The National Digestive Diseases Advisory Board has recommended that a clinical trial be initiated on PBC.

DIABETES AND PREGNANCY

Mr. Conte. As you know, Doctor, pregnancy causes major changes in hormonal regulation and metabolism in the mother and fetus. Diabetes is a common complication of pregnancy and can endanger the health of the infant. Is your institute looking at diabetes and pregnancy?

Dr. Gorden. The NIDDK shares with the NICHD a strong interest in the effects of diabetes on pregnancy. As a matter of administrative negotiation and tradition, our sister Institute provides the primary focus for research support in this area. However, this Institute does support a number of research grants concentrated on the most scientifically basic aspects of this problem. In addition, the National Diabetes Data Group, a function of the NIDDK, has examined the diagnostic criteria for gestational diabetes (diabetes occurring during pregnancy) and has published some new analyses on the relationship of this form of diabetes to more general forms of the disease.

The Diabetes Control and Complications Trial (DCCT) is a large, multicenter prospective clinical trial sponsored by NIDDK. While not initially conceived as a major thrust of the DCCT, data have been routinely collected on pregnancies occurring in women participating in the trial. Because of the large number of patients involved and the age of the cohort, the number of pregnancies that will occur over the course of the DCCT may exceed that of some major clinical trials undertaken with diabetes and pregnancy as the primary research question. Moreover, since DCCT metabolic and clinical assessments are routinely performed on all female subjects, extensive longitudinal data are available for both the pre- and postpregnancy periods. In recognition of the unique research opportunity presented, the DCCT study group is eager to enhance this aspect of the study. A subcommittee of study investigators is currently formulating a detailed study plan targeted to pregnancies occurring in DCCT female participants. Not only will these data speak to the issue of the effect of metabolic control on birth outcome, they will allow assessment of the effects of short-term preconception metabolic control versus long-term control. In addition, there is an opportunity to assess the effect of pregnancy on the long-term prognosis for diabetic complications in the mother, an issue now clouded by conflicting information.

Mr. Conte. Are you working with the Child Health Institute?

Dr. Gorden. The NIDDK is in frequent and close communication with the NICHD in areas related to diabetes and pregnancy. We jointly endeavor to avoid duplication of effort and provide complementary expertise. For example, the NIDDK has consulted with the NICHD for guidance in the planning of the pregnancy study within the DCCT that I mentioned previously.

AIDS RESEARCH

Mr. Conte. What are some of the major areas of AIDS research your Institute is involved with?

Dr. Gorden. The NIDDK supports AIDS research involving the effects of the human immunodeficiency virus (HIV) on the endocrine, digestive, genitourinary, renal, and blood cell systems. The Institute also supports research on the metabolic basis of the profound wasting and malnutrition that often hasten the death of AIDS patients and on basic mechanisms of HIV replication and integration, particularly those mechanisms that might provide a target for drugs or vaccines. In our intramural program, our world-premiere scientists who are experts in structural biology are using highly sophisticated X-ray techniques to determine the three-dimensional architecture of molecules in an intense search for anti viral drugs that may be useful in combating AIDS.

Mr. Conte. What spin-offs can we expect from your AIDS programs? Will this knowledge help in the other diseases your Institute is responsible for?

Dr. Gorden. The NIDDK expects that the AIDS research we support will contribute to improved therapy for HIV infection and AIDS; improved management of HIV-associated complications such as chronic diarrhea, kidney disease, and reduced levels of blood platelets; and improved patient survival resulting from better nutrition.

Knowledge gained through ongoing AIDS research is also likely to help advance research in other areas of interest to the NIDDK. For example, NIDDK researchers are currently preparing to test the use of dideoxyinosine, a compound developed by AIDS researchers, in a treatment regimen for Type C hepatitis. Type C hepatitis, which accounts for more than 90 percent of post-transfusion hepatitis, can result in permanent and potentially life-threatening liver damage.

AIDS research is also generating new knowledge about the workings of the immune system. Such knowledge may find widespread application in various diseases involving immune system abnormalities such as insulin-dependent diabetes.

OBESITY

Mr. Conte. Obesity is a major risk factor in the development of diabetes, high blood pressure, heart disease and stroke. What are you currently doing in looking at the underlying medical and social causes of obesity?

Dr. Gorden. The NIDDK's obesity research program consists of research projects supported by the extramural and intramural divisions of the Institute both in Bethesda and at our field station in Phoenix, Arizona. The Institute currently supports approximately 150 research projects, for over $20 million, related to obesity nationwide and is the primary NIH institute focused on obesity as a total disease entity. Research is focused on such areas as energy metabolism, control of food intake, fat cell biology, genetic and environmental factors, and therapeutic approaches to the treatment of obesity.

Enormous strides have been made by NIDDK scientists in Phoenix toward understanding the role of genetic and metabolic factors in obesity. For example, in research among the Pima Indian population, individual differences in resting metabolic rate have been observed, which suggest that this may be a factor in determining obesity. Accordingly, people with low metabolic rates are at higher risk for gaining weight than people with higher metabolic rates. It has also been shown that obesity is a familial trait that may be genetically determined.

Studies of obesity at the cellular level have uncovered a protein unique to the fat cell called adipsin. It is believed that this enzyme is involved in the regulation of fat cell metabolism. A greater understanding of how fat cells differentiate and are regulated will lead to new areas in the treatment of obesity.

New evidence on the enzyme lipoprotein lipase, which breaks down dietary fat so that it is used either for energy or reconverted to fat and stored in adipose tissue, implies that increased lipoprotein lipase activity may partially predispose individuals to regain weight following weight reduction.

Recent research suggests that the individual body composition parameters--fat mass and lean mass--are significant determinants of both sex hormone levels and cardiovascular disease risk factors. Thus, body composition--rather than body weight or relative weight--is important in determining energy expenditure and cardiovascular risk status.

Perhaps the most important recent breakthrough in understanding the harmful effects of obesity has come from analyses of fat distribution. It appears that fat concentrated in the abdominal area (the typical "male" pattern of fat) is more harmful than fat on the hips or thighs (the typical "female" pattern of fat). In both sexes, abdominal fat is associated with an increased risk for heart disease, stroke, high blood pressure, diabetes, and certain forms of cancer. These findings will guide investigators towards finding treatments of obesity aimed at decreasing abdominal fat and will help in identifying the factors that link obesity to its long-term health complications.

The highest rates of obesity are observed among the poor and minority groups, and particularly among Black women. Investigators at the NIDDK-supported Obesity Center are examining the underlying mechanism of obesity with the goal of reducing its prevalence and consequences in the Black population. To assist with this research effort is a New York based, non-profit organization which is recruiting subjects into the studies. Areas of investigation include possible defects in the way body heat is generated in Black women in comparison to White women, and differences in fat cell structure and/or fat cell metabolism between Black and White women. Such differences, if they exist, may predispose to the development of the complications of obesity in Black women. These studies will establish a link between the Obesity Research Center and the Black community and provide a foundation for future studies that will examine physiologic mechanisms leading to weight gain and the efficacy of weight reduction therapy.

Another promising study is being conducted at one of our Diabetes Research and Training Centers. Patterns of eating behavior are being investigated in a noninsulin-dependent diabetes mellitus population. This is being done to investigate and better estimate dietary compliance in a Black obese population where dietary compliance would markedly affect diabetes control.

PROSTATIC DISEASE

Mr. Conte. I'm pleased to know that you have been very involved in finding new methods of treating prostate enlargement and prostate cancer. What are some of the areas you're looking at in prostate research?

Dr. Gorden. The Urology Program of the NIDDK has the primary responsibility for research in the basic science of the regulation of prostate growth and the applications of that research to the clinical conditions of the prostate that affect the health of the population. Studies supported by the NIDDK are investigating the role of specific factors such as hormones and growth factors, which influence normal growth and abnormal enlargement of the prostate. Other studies are being conducted to determine the conditions present in both childhood and early adulthood, which initiate this abnormal growth pattern. A major goal of these research efforts is to provide techniques and therapies for early intervention that can detect the development of abnormal prostate enlargement at its initiation in the young adult years so that the growth can be arrested before it creates the troublesome and/or fatal conditions that develop in the aging male.

Mr. Conte. How much is currently spent on prostate disease research at your institute?

Dr. Gorden. In 1989, we spent $3,321,000 on prostate disease research.

AMYLOID AND DIABETES

Mr. Conte. I hear that you have discovered a molecule, amyloid, which interferes with the ability of cells to take in sugar. What is the clinical significance of this discovery?

Dr. Gorden. Microscopic collections of insoluble proteins called amyloid deposits have been observed in the pancreatic islets of elderly people, especially those patients with noninsulin-dependent diabetes mellitus, and in many benign tumors of the pancreas. This finding was first described many years ago. Researchers have recently isolated the predominant protein which makes up these insoluble deposits and named it islet amyloid polypeptide (IAPP) or "amylin." This protein is usually secreted by the insulin secreting cells (beta cells) of the pancreas at very low levels compared to insulin secretion.

The biological actions and therefore the clinical significance of IAPP are under extensive investigation at the present time. At extremely high doses, IAPP has been shown to inhibit insulin secretion. However, at more moderate doses, no significant effect has been observed on either the synthesis or secretion of insulin. Studies designed to examine the effects of IAPP on sugar utilization in whole animals have indicated that again at very high levels of IAPP an insulin-resistant state can be induced which is similar to what occurs in noninsulin-dependent diabetes. Thus, the issue remains unresolved as to whether the observed induction of an insulin-resistant state in an animal or man can occur at IAPP levels that can be observed in nature or only at levels which exceed those found even in a disease state such as diabetes.

Mr. Conte. Could it lead to improved medications or treatments?

Dr. Gorden. If IAPP is established to play an important role in the normal state and in diseases such as diabetes, then clearly it will offer a new mechanism for the control of sugar uptake by cells. This would likely result in an expansion of the opportunities available for development of medications or treatments that alter important metabolic processes relevant to diabetes.

ACCURACY OF SUGAR TESTS

Mr. Conte. Doctor, there has been concern over the accuracy of cholesterol measuring devices. What about glucose measuring machines? Are there any concerns over their accuracy?

Dr. Gorden. I am not aware of any systematic problems in the accurate measurement of glucose in clinical laboratory settings. The technology of glucose measurement by devices used by patients as part of self monitoring is still evolving and, of course, new devices must demonstrate their reliability. But this falls into the realm of the Food and Drug Administration regulatory functions and I have no authoritative information on this issue.

KIDNEY DISEASES

Mr. Conte. The kidney is a key regulator of salt and water balance for the body. What is the extent of research investigating electrolyte and fluid imbalances caused by kidney disease?

Dr. Gorden. The kidney maintains very close control over the amount of salt and water in the body. This is a very complex process, and we are still conducting most of our studies on how this functions under normal conditions.

It is vitally important for the survival of an organism that both the osmotic concentration and the volume of its "internal environment," the extracellular fluid, be maintained constant. Since sodium (salt) and its attendant anions are the major osmotic constituents of the extracellular fluid, the organism must control the amount of salt as well as the amount of water in this fluid. The is done primarily by controlling the rate of excretion of these substances; control of the intake of salt and water is usually, but not always, of secondary importance.

Within the kidney, the rate of excretion of salt and water is controlled by regulation of the glomerular filtration rate (GFR) and by regulation of the rate of tubular reabsorption. To a great extent, water reabsorption occurs as mechanisms involved in the maintenance of the osmotic concentration and volume of the extracellular fluid are the active transport systems for salt. The functioning of these systems and their influence on water reabsorption are affected by the anatomic structure of the various parts of the nephron, the activity of the other transport systems within the nephron, and a variety of chemical and physical factors that arise from both inside and outside the kidney.

Renal concentrating and diluting ability is frequently impaired early in renal disease and it is always affected in advanced generalized renal diseases when renal failure results. Many diseases affect renal function, but we are just beginning to study them. Examples of diseases that affect water handling include chronic pyelonephritis or medullary cystic disease. Less common are diseases characterized solely or predominantly by impairment of either renal concentration or renal dilution. Our intent is to bring the newly developed knowledge of normal kidney function to this study of kidney function in specific kidney diseases. However, the field of inquiry is in its infancy.

Mr. Conte. Dr. Gorden, as you know, glomerular diseases, especially glomerulonephritis, are a complex and challenging field of research. What are some of the future prospects in looking at glomerular diseases and nephrotic syndrome - a key complication?

Dr. Gorden. Glomerulonephritis is a term referring to a multiple glomerulus. Some are genetic in origin, and others are due to acute diseases, which resolve spontaneously. The ones which lead to end-stage renal disease are characterized by inexorable progression of a chronic scarring process leading to obliteration of the whole kidney. The process is often associated with the loss of a larger amount of protein in the urine due to the glomerulare abnormalities.

Therefore, the future prospects for research in glomerulonephritis and the nephrotic syndrome are tightly linked. The causes of glomerulonephritis are largely unknown, but include immunologic disorders, as noted above. Therefore, NIDDK is emphasizing studies at the basic cell and molecular level of the normal and abnormal glomerulus. These include the composition and stimulation of its basement membranes, its responses to metabolic and immunologic injury, and the mechanism of cellular injury and repair.

Another condition which causes glomerulonephritis and nephrotic syndrome is the idiopathic nephrotic syndrome. It is a disease where the nephrotic syndrome develops in the absence of any other underlying disease. Congenital nephrotic syndrome is an inherited disorder. To date, investigations have provided only detailed morphologic descriptions of certain components of the glomerulus, in this and other inherited disorders. However, at present, we do not yet understand the molecular basis of any of these disorders. In childhood, the steroid-resistant type of nephrotic syndrome (focal segmental glomerulosclerosis) represents a common cause of chronic renal failure. Overall, the incidence of renal failure is 25-30 percent by 5 years after the onset of the disease and 30-40 percent after 10 years.

Unfortunately, currently there is no documented effective treatment for children with disorders such as steroid-resistant nephrotic syndrome and focal segmental glomerulosclerosis.

Caring for children with chronic illness is a challenging as well as frustrating experience for the family, physician and society. Nephrotic syndrome is no exception.

Concerted research efforts are clearly needed to allow us to understand the underlying mechanism resulting in chronic renal diseases and to be able to finally control or halt progression to chronic renal failure, and curtail the enormous human and economic suffering to which chronic renal disease leads.

GRAVES' DISEASE

Mr. Conte. Are there any new developments in the diagnosis and treatment of Graves' disease?

Dr. Gorden. Graves' disease is an autoimmune disorder involving the thyroid, the eyes and, less commonly, the skin. Although many questions remain about the fundamental immune processes involved in its pathogenesis, very successful strategies are available for the diagnosis and treatment of the thyroid component of the disorder. Antithyroid drugs, radioactive iodine and surgery are all highly successful in correcting the thyroid dysfunction. Because a randomized, controlled comparison of these therapies has not been done, individual endocrinologists have variable opinions on the relative merits of these therapeutic options. Recent advances in measuring thyrotropin allow sensitive adjustment, and usually complete normalization of thyroid hormone levels in patients with Graves' disease.

Now that sophisticated orbital imaging techniques are available, it has become apparent that the vast majority of patients with Graves' disease have some eye involvement. Usually this results only in mild discomfort, swelling or protrusion of the eyes. However, about 3% of Graves' disease patients have severe progressive eye disease which can compromise vision. Unfortunately, therapy of the eye component of Graves' disease remains problematic. Prednisone and other anti-inflammatory, immunosuppressive drugs are often effective, but at the cost of significant side effects. Response to radiation therapy is variable. Severe cases may require decompression surgery to preserve vision. It is hoped that new understanding of pathogenesis will lead to the development of more effective therapy for the eye component of Graves' disease.

PARATHYROID

Mr. Conte. The parathyroid is a major regulator of calcium and is involved in several genetic based tumors. Where are we in the search for the gene and growth factor responsible for familial multiple endocrine neoplasia, type I?

Dr. Gorden. Familial multiple endocrine neoplasia-type I (MEN-I) is an inherited disease, the result of an autosomal dominant gene defect. It produces tumors or hyperplasia in multiple endocrine organs; the parathyroid glands, the anterior pituitary gland, and the endocrine pancreas may all be involved in varying degrees. MEN-I is seen in approximately 1 in 6000 individuals. When detected in one individual it is usually also found in first and second degree relatives. Recently, exciting new information has been developed about this disease by intramural scientists at NIDDK. They found that the putative gene causing MEN-I is located on human chromosome 11. They have come to within 2-3 million bases of its location and are working on narrowing the location so that they may isolate it, much as was done recently for the cystic fibrosis gene. In addition, they have isolated a growth factor from the plasma of affected individuals, which may be involved in the transformation of susceptible tissues containing the mutated gene into neoplastic tissue. Indeed, the current hypothesis is that two events are required for transformation in the generation of tumors, one of which is related to the mutated gene, the other perhaps to this growth factor. They postulate MEN-I may be analogous to retinoblastoma, where the genetic mutation results in the loss of a gene whose product suppresses tumor formation. Work is currently underway to isolate and study the causative factors in MEN-I. This work is important not only for understanding this rare genetic disease but for elucidation of basic mechanisms of tumorigenesis that may shed light on causation of other benign and malignant tumors.

DIABETES IN MINORITIES

Mr. Roybal. Please provide a list of the projects or grants presently being funded by NIDDK to deal with the problem of diabetes in minorities. Please identify which minority group is being impacted by the specific research projects.

Dr. Gorden. The NIDDK supports many projects specifically dealing with diabetes in minorities. Examples of these projects include:

R29 DK 41969 - Cardiovascular and Metabolic Health in High Risk Youth (Blacks). Principal Investigator, Cindy Hanson.

R01 DK 32767 - Predicting Gestational and Subsequent Overt Diabetes (Blacks). Principal Investigator, Ronald Acton.

N01 DK 72292 - Center for Diabetes, Arthritis, and Renal Disease in the Gila River Indian Community (Pima Indians). Principal Investigator, Viola Johnson.

R22 DK 31170 - Japanese American Community Diabetes Study (Japanese). Principal Investigator, Wilfred Fujimoto.

R01 DK 40414 - Obesity in Black Women (Blacks). Principal Investigator, Xavier Pi-Sunyer. (This grant is diabetes-related.)

N01 DK 62285 - Coordinating Center for Diabetic Renal Disease in the Pima Indian Population (Pima Indians). Principal Investigator, George Williams.

R01 DK 38392 - Diabetes-related End-stage Renal Disease: Ethnic Comparisons (Blacks and Mexican Americans). Principal Investigator, Jacqueline Pugh.

N01 DK 72271 - Evaluation of Diabetic Renal Disease in the Pima Indian Population (Pima Indians). Principal Investigator, Bryan Myers.

R01 DK 34818 - Epidemiology of Diabetic Complications (Many minorities). Principal Investigator, Trevor Orchard.

Y01 DK 70111, 70112, and 70113 - Interagency agreements with the National Center for Health Statistics for HANES III (Many minorities).

In addition, extensive research on diabetes in the Pima Indian population has been conducted for over 20 years at the NIDDK's intramural field station in Phoenix, Arizona.

Our Diabetes Research and Training Centers also support several projects that relate to diabetes in minorities, including a program aimed at weight control for obese Blacks with noninsulin-dependent diabetes, a study of eating patterns in a Black obese population, and an examination of the screening process used for diabetics at urban primary care clinics in New York.

Mr. Roybal. Diet is a major factor in dealing with diabetes, especially among minority persons. What initiatives are you conducting to address the issue of diet and nutrition information in minority communities? What initiatives do you have planned in FY 1991.

Dr. Gorden. A major function of the Diabetes Research and Training Centers (DRTC), through their training and translation program, is to generate the most competent professional personnel, and to translate advances in the field of diabetes research with the least delay into improved care for the diabetic. For example, at the Vanderbilt DRTC, a study is being conducted to investigate patterns of eating behavior in a black obese population where dietary compliance would markedly affect diabetes control. From computer analysis of data recorded in patient diaries, compliance and certain other clinical data will enable investigators to evaluate this method before the technique is recommended for standard assessment practice in minority diabetes education.

A study at the University of Chicago DRTC will develop a program in lifestyle modification in an obese minority (predominantly Black) population with Type II, noninsulin-dependent diabetes (NIDDM). The aims of this study are to develop a program that assists these minority group patients in changing lifestyles that will lead to weight loss and improved metabolic control, and package the program so that it can be widely disseminated.

Studies at the Albert Einstein DRTC in the Bronx, New York, are evaluating the screening process used by health care professionals for people with Type II diabetes in federally-funded urban primary-care clinics. Results to date indicate that assessment of risk factors for the vascular complications of diabetes is not routinely performed in urban primary-care centers. In addition, nutrition information that could lead to weight control and improved vascular outcome is not being provided. This information should prove useful in providing an impetus for more intense efforts in this area.

The NIDDK's National Diabetes Information Clearinghouse distributes printed materials to diabetes health educators and health professionals who conduct programs for Blacks and Hispanics with Type II diabetes. These materials include: "Diabetes Dateline," The Diabetes Dictionary, Noninsulin-Dependent Diabetes, Spanish Language Materials for People with Diabetes: A Bibliography, and Diabetes and Kidney Disease: Selected, Annotated Bibliography. The Diabetes Clearinghouse is also developing a resource guide entitled, "Diabetes in Blacks," which will provide descriptions of programs and materials targeted to this audience.

The Institute has sponsored and participated in several conferences and workshops in the past two years that addressed Diabetes in the Black Population, Diabetes in Native Americans and Alaska Natives, and Diabetes in Hispanics. Speakers at the second national conference on Diabetes in the Black Population emphasized the importance of health professionals and the Black lay community in conveying an important message. That message, directed particularly to Black women, should underscore that obesity is a major risk factor for diabetes. They must understand that they can take charge of their own behavior and achieve weight loss.

Plans for future initiatives include research on control interventions for the prevention and treatment of diabetes in minorities. Instituting effective weight control programs may prevent the frank emergence of diabetes in a young adult at risk for diabetes and may prevent or lessen complications in the person who already has diabetes. In addition, the NIDDK and the Indian Health Service have planned a collaborative effort to study NIDDM in Native Americans and Alaska Natives and have recently signed a Memorandum of Understanding to advance this effort.

Mr. Roybal. How much funding is available in your budget request for information dissemination on diabetes?

Dr. Gorden. Including the National Diabetes Information Clearinghouse, the education components of the Diabetes Research and Training Centers and direct public information activities, we estimate that we will spend about $615 thousand on diabetes information dissemination in 1991.

Mr. Roybal. What is the incidence of diabetes among Blacks, Hispanics, Asians and Native Americans? How does this compare to the total population?

Dr. Gorden. We now have very accurate data on the number of people with diabetes in these four racial/ethnic groups, and we find considerably higher rates of diabetes in these groups compared to the total population. Diabetes in Blacks is 60 percent greater than in the general population. Mexican Americans in the southwest United States have twice as much diabetes as the total U.S., and similarly high rates are found among our Puerto Rican population in the New York City area and in the island of Puerto Rico. Prevalence of diabetes among Japanese-Americans in Washington State and California is also about twice the national rate. Our Native American tribes have some of the highest rates of diabetes in the world. Among the Pima Indians of Arizona, for example, 50 percent of adults have diabetes. The Seminole and Creek Indians of Oklahoma, the Papago of Arizona, Passaquoddy of Maine, Plains Indians of Montana and Wyoming, Mohawk of New York, Chippewa of Minnesota, and Seminole of Florida are some of the other tribes that bear an increased burden from diabetes. Recent data on Native Americans in the northwest States of Washington, Oregon, and Idaho indicate that they may have three times as much diabetes as found in the general population. We are particularly concerned about diabetes in our Alaskan Natives. While diabetes appeared to be rare among Alaskan Eskimoes 20 years ago, current studies indicate that rates have increased dramatically.

Mr. Roybal. How much of your budget is directed toward diabetes among minorities? How does this compare to the incidence of the disease among this group?

Dr. Gorden. The NIDDK is the lead Institute for diabetes research at the NIH. In our 1991 budget request we show $157.7 million for diabetes and related research. This research covers an array of important general problems in diabetes, such as: the role of the immune system and possible immunosuppressive therapies, genetics of diabetes, understanding of the cellular processes of insulin secretion and action and glucose transport, and investigation of the complications of the disease. Advances in understanding and treatment of diabetes will have a major effect on the health of minority populations, because the prevalence of diabetes in these groups is substantially greater than in the general population -- in many cases two fold higher or even more.

RESEARCH CENTERS

Mr. Stokes. Your request for centers is for level funding of 40 centers at $33.8 million. At this level of funding, would you choose to reduce the number of centers or drastically reduce the budgets of all currently supported centers?

Dr. Gorden. We are beginning to seriously consider reducing the number of centers in order to more adequately support the remainder. However, this cannot be done until a group of centers in one program compete for renewal support. This will not be the case for most of the centers programs in 1991, so we will be making cuts below the recommended levels of support.

Mr. Stokes. Under the President's Budget, what amount of downward negotiation would be required for centers?

Dr. Gorden. The downward negotiations would average about 30 percent in 1991.

Mr. Stokes. In your professional judgement, what is the appropriate level of funding for centers?

Dr. Gorden. Full funding of all current centers would require $48.2 million.

ROLE OF DIET IN KIDNEY FAILURE

Mr. Stokes. I understand that your Institute is studying the role of diet in kidney failure, which is a major health problem and is a very serious problem among Blacks. Has the cost of this study had a major impact on your grant program?

Dr. Gorden. I believe you are referring to the major NIDDK clinical trial, in cooperation with the Health Care Financing Administration, on the "Modification of Diet in Renal Disease" or MDRD. The primary goal of this Congressionally-mandated study is to determine whether low protein and low phosphorus diets can slow the progression of chronic renal disease to irreversible kidney failure or end-stage renal disease (ESRD). This is a very important study because it is exploring promising research leads that offer hope of improving the quality of life for thousands of kidney disease patients, many of whom are minorities. In addition, the results of the study could have a significant positive impact on the Federal Medicare costs of providing kidney dialysis and kidney transplantation to ESRD patients. These costs are now approaching $4 billion annually, and could be reduced substantially if the need for dialysis and transplantation could be deferred or eliminated.

In Fiscal Year 1989, the impact of the MDRD on our regular research grant program was significant. As a result of the MDRD costs, we awarded about 30 fewer regular research grants than we would have if we had not had the clinical trial. In Fiscal Year 1990, the cost of this study is approximately $6.9 million. In Fiscal Year 1991, this cost will increase to $10 million.

LIVER TRANSPLANTATION

Mr. Stokes. Can you give us an update on the state-of-the-art of liver transplantation? How successful is this technique? How successful has transplantation of only part of the liver (vs. the whole liver) been?

Dr. Gorden. Liver transplantation has advanced enormously in the last 10 years. Last year, 1,681 liver transplants were performed in the United States in approximately 50 different transplant centers. The average one-year survival rate after liver transplantation is about 70 percent, but for some diseases the one-year survival rate has been greater than 90 percent, and thus similar to that for kidney transplantation. The majority of patients return to a fairly normal life style and many are able to return to productive work.

About three-fourths of transplants are done in adults and the rest in children. The major reasons for liver transplantation in adults are primary biliary cirrhosis, sclerosing cholangitis, chronic autoimmune hepatitis, chronic hepatitis C, chronic hepatitis B and alcoholic liver disease. Other important but less common reasons for liver transplantation have been liver failure from acute hepatitis and liver cancer. In children, the major reason for liver transplantation is biliary atresia, a congenital disease in which the bile ducts waste away and the liver eventually becomes cirrhotic. Before liver transplantation, most children with biliary atresia died before the age of five. At present, most children undergo liver transplantation and can lead a fairly normal life.

One of the major shortcomings in the field of liver transplantation today is a shortage of organs. This is particularly a problem with transplantation of children. The reason for this is that the organ that is placed into the patient must be approximately the same size as the organ that is removed, so that one cannot use an adult liver in a child. Until recently, at least 25 percent of children with biliary atresia died while waiting for a liver transplant. This is now changing with the development of the "segmental" liver transplant in which an adult liver is pared down to size to fit into a child. These partial or segmental transplants have been very successful and have allowed for more and more children to benefit from liver transplantation.

In studies from the University of Chicago, the one-year survival after segmental liver transplants was the same as after full size transplants (about 70 percent) and the waiting period for a transplant in children has dropped by more than half.

SICKLE CELL ANEMIA

Mr. Stokes. Your justification tells us that NIDDK and NHLBI investigators recently found a drug that would activate fetal hemoglobin genes in severely affected sickle cell anemia patients. Can you tell us more about this?

Dr. Gorden. Sickle cell anemia is a painful and incurable blood disease, with potentially fatal outcome, affecting an estimated 60,000 Afro-Americans, and millions of others around the world. It results from a genetically abnormal form of hemoglobin, which has a reduced ability to carry oxygen to the tissues, and causes the blood cells to stiffen and clog blood vessels.

A promising area of drug research involves hydroxyurea, a prescription product used to treat some forms of leukemia. Early tests in sickle cell anemia patients by NIDDK and NHLBI investigators, and at seven university hospitals, have demonstrated that in the presence of a significantly increased production of fetal hemoglobin, less sickling occurs. This exciting finding provides the likelihood of markedly reducing the symptoms of the disease.

In a follow-up study, these investigators are combining hydroxyurea with a growth factor called erythropoietin to see if the two drugs together are more effective than hydroxyurea alone.

In addition, development of genetic therapy could have a significant effect on sickle cell treatment. NIDDK investigators and others have inserted the genetic defect that causes sickle hemoglobin into mice, and are close to developing a true animal model that could be used to study drugs and other treatments. Investigators also are working to perfect the techniques that could be used to insert normal hemoglobin genes into the chromosomes of sickle cell anemia patients, thereby curing the disorder, as well as preventing the symptoms.

RESEARCH GRANTS

Mr. Early. Dr. Gorden, what percentage of new and competing grants will be funded under the FY 91 budget request?

Dr. Gorden. In 1991 we will be able to fund about 26 percent of the approved research grant applications.

Mr. Early. And how does this compare to FY 90 and FY 89?

Dr. Gorden. In 1989 we funded 29 percent of the approved research grant applications, and for 1990 we estimate the funding rate at 22 percent.

Mr. Early. Doctor, a few years ago, you were funding over 30 percent of approved grants, weren't you?

Dr. Gorden. Yes, every year until 1989.

Mr. Early. To what payline percentile will you fund the FY 91 request?

Dr. Gorden. We estimate that the payline will be about the 20th percentile in 1991.

Mr. Early. And how does this compare with the past couple of years?

Dr. Gorden. Before 1989 we had always had a payline above the 30th percentile. In 1989 the payline was the 24th percentile, and in 1990 we estimate it will be about the 17th percentile.

Mr. Early. Can you give us some idea of what this percentile ranking means in terms of priority score?

Dr. Gorden. Although there is no absolute correlation between percentile rank and priority, the 24th percentile in 1989 would be a priority score of about 150; the 20th percentile in 1991 would be a priority score of about 145.

Mr. Early. What effect has downward negotiation had on the research that's supposed to be conducted with these grants? What effect has this had on NIDDK's research program -- both short-term and long-range?

Dr. Gorden. As you know, when study sections approve grants in the peer review process, they recommend an award amount that they think is the right dollar amount to permit the investigator to carry out the research he or she has proposed. Often the amount the study section recommends is already lower than the investigator originally requested. For example, a study section may delete a technician or a specific piece of equipment from the budget supplied by the investigator in the grant application. In addition, the Institute advisory council may review the study section approved level and decide to cut it further.

When the Institute awards an approved project, the actual level of funds is then negotiated downward from the approved level, not from the level the investigator initially requested. So, in some extreme cases, you might have the study section making cuts, the Council making more cuts, and then a downward negotiation tacked on top of those.

The final effect on the investigator in the short term is to ask him or her to do a project with less than is needed. Often this means in practical terms that the research will take longer to complete because fewer persons are involved on the team or because needed equipment cannot be purchased. Sometimes it means that a whole approach to a project must be eliminated from the study. Thus, the pace and scope of the research are reduced.

The long-range effects of these cuts are not only on the speed and diversity of research, but also on the manpower. If an investigator cannot support a graduate student or post-doctoral fellow on a downward-negotiated grant, that developing researcher may be permanently lost to the research community. So you are not just putting off research for a while, you are actually cutting off the people who are in the process of becoming independent investigators for the future.

Mr. Early. What happens to the research project in non-competing status? The grant was approved. The grant budget was reviewed, adjusted downward by the review panel, and then approved -- at an amount deemed appropriate for carrying out the research. The project is under way at this point. What happens?

Dr. Gorden. When an award is made on a new research project, that award is then subject to downward negotiation at the same rate as other newly awarded grants in that fiscal year. In subsequent years, downward negotiations may occur at a different rate, but they are applied against the fully-funded award level. So you don't get a snowball effect where a grant is cut by 10 percent more each year until there's nothing left. This is the fairest way we can think to do this, but it complicates research planning even further, because next year your grant budget may be cut at a different level. This makes it extremely difficult for the investigator to plan and conduct a research program effectively and efficiently.

RESEARCH CENTERS

Mr. Early. Since this has not been a single year occurrence, what effect will this downward negotiation have on the Centers and their research programs?

Dr. Gorden. For the past several years, NIDDK Centers have been subject to negotiated downward reductions of up to 25 percent from study-section approved levels, and these downward negotiations are projected at 30% under the FY 1991 budget request. Reductions of this magnitude seriously compromise the NIDDK Centers as they were originally conceived. Effects of underfunding have resulted in such hardships as limiting the numbers of pilot studies which attract promising young researchers; forcing choices between the deletion of research resource cores or decreased funding; being unable to maintain and upgrade equipment; the necessity to dismiss personnel in some cores; the inability to develop new specialized cores, such as in molecular biology, which provide the important tools in the advanced technological environment of research today; and not having sufficient resources for training and educational activities.

Mr. Early. To what extent is NIDDK clinical research supported by the Centers Program? Are you in a situation similar to NLHBI's?

Dr. Gorden. Most NIDDK clinical research is supported through the regular research grant and research contract mechanisms. For example, in FY 1989, the NIDDK expended approximately $30 million on clinical trials that were conducted largely through those mechansims, as well as some small studies in the NIDDK intramural program.

However, research centers provide an important research resource for clinical investigators who work on regular research grants or research contracts at the institutions at which the centers are located. The centers provide centralized research resources that these investigators can use, as well as opportunities to engage in important pilot and feasibility studies, through which an investigator can test new innovative ideas and collect preliminary data that will assist him in competing for a subsequent regular research grant.

The Centers constitute an important part of the NIDDK research portfolio. The President's budget projects that NIDDK will fund 40 centers in FY 1991 at approximately $33.7 million. These centers include Core Centers (P30), Specialized Centers (P50), and Comprehensive Centers (P60). Clinical research activities comprise approximately 15 to 20 percent of the NIDDK Centers Program. Although this centers mechanism is not the major avenue through which the NIDDK supports clinical research, it is a very important avenue for developing innovative research ideas. As is the case in many of the other NIH Institutes, the NIDDK Centers have been impacted by the downward negotiated funding levels which will most certainly reduce the size, scope, and pace of the centers research program. Components of the centers research program that are likely to be affected by negotiated reductions include pilot and feasibility studies, model diabetes training and translation activities, and shared research resources.

Mr. Early. What is the estimated full cost for research centers in FY 91?

Dr. Gorden. The estimated cost for fully funding the NIDDK's research centers without downward negotiations in FY 1991 is $48.2 million.

CLINICAL TRIALS

Mr. Early. Will NIDDK be able to start any new clinical trials in FY 91.

Dr. Gorden. We will continue our current clinical trials but will not initiate any new ones at the FY 1991 budget request level.

Mr. Early. Are there high priority clinical trials which are ready but cannot be initiated because of the lack of funds in the FY 91 request? If so, please provide a list of these for the record, along with a brief description and the associated cost, including first year cost.

Dr. Gorden. The following is a list of 18 clinical trials which could be initiated if additional funding were available.

New Clinical Trials That Will Not Be Undertaken in FY 1991
(in thousands)

Title	Est. 1st Yr Cost	Total Proj. Cost
Diet and Exercise in the Prevention and Treatment of Noninsulin-dependent Diabetes Mellitus	$1,500	$6,000
Clinical Study of Gallstone Recurrence Following Extracorporeal Shock-Wave Lithotripsy	1,000	6,000
Use of Recombinant Human Erythropoietin in Adult and Pediatric Patients with Renal Failure	1,000	5,750
Clinical Trials in the Treatment of Primary Biliary Cirrhosis	2,000	14,000
Comparison of Therapeutic Modalitites in the Treatment of Interstitial Cystitis	1,000	5,750
Comparison of Surgery Versus Medical Follow-Up in Asymptomatic Hyperparathyroidism	1,000	10,000
Clinical Trial of Prevention and Therapy of Hypertensive Renal Disease in Blacks	2,000	11,500
Enzyme Replacement Therapy in Inherited Metabolic Diseases	1,000	6,500
Immunosuppressants in Crohn's Disease	1,500	8,500
Effective Weight Loss Strategies for Obese Diabetics in High Risk Minority Populations	1,500	6,000
Liver Transplantation Trials Using Alpha Interferon, PGE-1 in Severe Viral Hepatitis; Monoclonal Antibodies to Prevent Reinfection in Hepatitis; and Salmon Calcitonin After Liver Transplantation in Primary Biliary Cirrhosis Patients	1,200	2,500
The Efficacy of Alternative Therapies for the Treatment of Symptomatic Benign Prostatic Hyperplasia	1,500	9,000
Peptic Ulcers: Role of Helicobacter Pylori	3,000	8,000

The Long-Term Effects of Extracorporeal Shock-Wave Lithotripsy on the Kidney and Other Organs	1,500	8,000
Immunotherapy for Pre-Type I Diabetics	1,000	5,000
Comparison of Amino Acid and Ketoacid Analogues to Essential Amino Acids as Nutritional Supplements for Protein Restricted Diets	2,000	11,500
Comparison of Radioiodine Versus Anti-thyroid Drug Therapy in Graves' Disease	750	8,000
Effect of Diet on Lipid Levels in Diabetic Patients	800	3,000
TOTAL	$25,250	$135,000

KIDNEY DISEASE OF DIABETES MELLITUS

Mr. Early. Doctor, how much is being allocated in FY 90 for kidney disease of diabetes mellitus? In FY 91?

Dr. Gorden. The NIDDK estimates that it will spend $9.9 million in FY 1990 for research on the kidney disease of diabetes mellitus. In FY 1991, the Institute expects to increase this figure to $10.3 million.

Mr. Early. I understand that a request for applications has been issued. What has been the response?

Dr. Gorden. In FY 1990, the NIDDK made nine additional grant awards on a previously issued RFA to study the kidney disease of diabetes mellitus (KDDM). The Institute also issued a new RFA on KDDM in January, 1990. Although the April application deadline for this new RFA has not yet arrived, we have heard from our grantees that many are planning to apply and compete for our grants under this research solicitation.

INTERSTITIAL CYSTITIS

Mr. Early. What progress can you report on research on interstitial cystitis?

Dr. Gorden. NIDDK currently supports 11 grants for research on interstitial cystitis (IC) for a total amount of greater than $1.8 million. The scope of the research has expanded to include six grants on the clinical aspects of the disorder and five on the basic science aspects. Areas of investigation include investigation of the coating materials of the bladder lining that prevent disease formation, comparison of bladder material in patients with IC with those of unaffected patients, and the investigation of specific substances found in the bladder of patients with IC. Many of these grants were initiated by recent program announcements and requests for applications. At a scientific workshop on IC to be held in May

1990, in conjunction with the Interstitial Cystitis Association, 17 investigators will present new data on specific IC research. Included in the presentations at this workshop will be reports of clinical trials for the therapy of IC. A pilot database has been funded to evaluate the best method for acquiring quantitative and qualitative data on interstitial cystitis. This pilot database utilizes a newly developed set of diagnostic criteria.

Mr. Early. To what extent will you be able to implement the 5-year plan to develop research on IC given NIDDK's FY 90 funding level and FY 91 budget request?

Dr. Gorden. NIDDK will continue to implement the 5-year plan utilizing the FY 1990 funding level and FY 1991 budget request. The major impact of limited funds will be on funding of research grant applications. Because the NIDDK is committed to funding the best research, it will necessarily restrict grant funding to those that receive the best recommendations from the peer review study sections. Designation of funds specific for IC research would allow the NIDDK to expand the number of grant applications that will be funded during FY 1991.

CYSTIC FIBROSIS

Mr. Early. What are your plans in the area of cystic fibrosis research for FY 90 and FY 91? How much do you plan to allocate for cystic fibrosis research in FY 90 and FY 91?

Dr. Gorden. The Cystic Fibrosis Program of NIDDK supports one Core Cystic Fibrosis Research Center (P30) and four Specialized Cystic Fibrosis Research Centers (P50). These centers foster a coordinated multidisciplinary approach to research in cystic fibrosis and provide support for pilot and feasibility studies. The program also supports individual research grants on both basic and clinical studies of cystic fibrosis with special emphasis on characterization of the recently identified cystic fibrosis gene, its protein product and the relation to the known defect in chloride ion transport which occurs in cystic fibrosis. A request for applications, "Research on the Molecular Basis of Cystic Fibrosis" has just been released by NIDDK to capitalize on identification of the major cystic fibrosis gene mutation. This program will augment the ongoing NIDDK research program in cystic fibrosis by providing an opportunity for investigators to address questions related to the etiology and pathophysiology of cystic fibrosis in light of these recent findings.

Our plans are for $10.6 and $11.1 million to be spent on cystic fibrosis research, respectively, in FY 1990 and FY 1991.

Mr. Early. Will you be able to strongly support the Cystic Fibrosis Centers given your budget problem?

Dr. Gorden. The NIDDK is funding its five Cystic Fibrosis Centers in FY 1990 at a total cost of $3.37 million, and anticipates being able to maintain this level of support in FY 1991. At this level of support the amount actually awarded to each center was significantly reduced from the amount recommended by scientific review groups. We anticipate a continued requirement for such reductions in the recommended budget for each center. We have recently limited the maximum budget our Core Cystic Fibrosis Research Center is allowed to request at its next competitive renewal application.

UNDIAGNOSED DIABETICS

Mr. Early. I understand that diabetes afflicts more than 11 million individuals, and that half of these individuals remain undiagnosed. What is NIDDK doing to address this situation?

Dr. Gorden. In order to identify undiagnosed diabetics, who may have no symptoms, it is vital that physicians be aware of the magnitude of this group and of the importance of early diagnosis. NIDDK supports two major different types of efforts that are especially valuable in this regard.

The NIDDK has established the National Diabetes Information Clearinghouse to serve as a national focus for collection and distribution of information about diabetes. This organization serves as a resource in determining the existence and location of useful educational material in diabetes and in assisting health professionals and the public to obtain such material. In addition, the Clearinghouse has developed educational materials that are provided to organizations for health professionals, such as the American Association of Diabetes Educators, and to the general public. Professional groups use materials obtained through or generated by the Clearinghouse in programs to inform the public of diabetes symptoms, complications, and treatment. Among the many publications available from the Clearinghouse are a bibliography of Spanish language materials, and a newsletter announcing meetings, special events, and new publications. A resource guide entitled "Diabetes in Blacks" is also under development.

In addition, NIDDK supports six Diabetes Research and Training Centers. One of the key components of these centers is to provide for transfer of information of the highest quality to current medical practice in a form that is applicable and available to the spectrum of health professionals providing health care to people with diabetes. The centers play an active role in raising the level of knowledge about diabetes in the professional community. In addition, the centers fund pilot projects in areas that relate to diabetes, such as weight control. These projects eventually may result in new programs that can be transferred to the appropriate agency for implementation. As an example of this type of activity, the University of Chicago Diabetes Research and Treatment Center is developing a program to assist minority group patients in changing lifestyles to promote weight loss and improved metabolic control.

Private sector groups and voluntary organizations also seek to increase public awareness of the scope and impact of diabetes. The NIDDK works in close cooperation with groups such as the Juvenile Diabetes Foundation and the American Diabetes Association, which actively publicize information about diabetes.

IMPLANTABLE INSULIN PUMP

Mr. Early. When do you expect the implantable insulin pump to become available?

Dr. Gorden. The implantable insulin pump that I believe you are referring to is the PIMS pump developed with the support of the NIDDK at Johns Hopkins and the Applied Physics Lab in Baltimore, Md. This device is presently in clinical trials that are required before it can be made generally available. As you know, the NIDDK is not directly involved in the regulatory process for medical devices, but we continue to follow the research aspects of this technology. To the best of my knowledge, the clinical trials are proceeding well and the device appears to be performing up to expectations. I would expect that there are still several years of testing to be done but, providing no major problems develop, commercial availability is within sight. The NIDDK also continues to support several other projects related to insulin pumps, including grants to the biotechnology industry through our Small Business Innovation Research program.

RESEARCH ON STEROIDS

Mr. Early. Doctor, given the spotlight on the issue of drug abuse, I was wondering if your institute supports research on the effects of the use of steroids, particularly by young athletes?

Dr. Gorden. At the present time, the NIDDK supports some fundamental research on anabolic steroids, specifically looking at the biological mechanisms of action of these substances and problems with steroid metabolism. The Institute, however, does not currently support research on the use of steroids by athletes.

NEW IMMUNOSUPPRESSIVE DRUG

Mr. Early. In the area of liver transplantation, I understand a new drug (FK-506) has been developed. Tell us a little about this new drug.

Dr. Gorden. FK-506 is a medication that was developed by the Fujisawa Pharmaceutical Company in Japan about five years ago. This company was looking for new drugs that suppress the immune system. Because of its promise in treating organ rejection, FK-506 was then extensively investigated by NIDDK grantee, Dr. Thomas Starzl, and his co-workers at the University of Pittsburgh. They showed that FK-506 was 100 times more potent than cyclosporin [the immunosuppressive medication that is currently used in transplantation] and that FK-506 prevented rejection in several animal models. Dr. Starzl obtained permission to use FK-506 in humans in March 1989. The early results were startling: FK-506 reversed severe organ rejection after failure of all other medications. Furthermore, FK-506 could be used as a single agent to prevent rejection and was safer and better tolerated than cyclosporin and prednisone. Dr. Starzl has worked closely with the Fujisawa Company and the Food and Drug Administration (FDA) to put FK-506 on the "fast track" for possible licensure by the FDA for use in organ transplantation. A controlled trial of FK-506 has begun in Pittsburgh and a large, multicenter controlled trial comparing FK-

506 to cyclosporin for liver transplantation is now being designed in collaboration between NIDDK and three large transplantation centers.

FK-506 may also have important uses outside of organ transplantation. In particular, FK-506 may be an ideal drug to treat the so-called "autoimmune" diseases, such as Type I diabetes, rheumatoid arthritis, lupus erythematosis, ulcerative colitis, Crohn's disease, primary biliary cirrhosis and sclerosing cholangitis (to name just a few). These are diseases for which there are now no satisfactory treatments and they cause severe disease in many patients. The possible role of FK-506 in treating autoimmune diseases is very exciting and has led NIDDK staff to begin discussions and collaborations with the Fujisawa Company, the Food and Drug Administration, Dr. Starzl and our grantees to set up trials of this agent in these important diseases.

NEW INITIATIVES IN 1991

Mr. Early. Will any significant new research initiatives or opportunities be lost or delayed due to lack of funds in the FY 91 budget request?

Dr. Gorden. There are many worthwhile research activities that have been recommended to us by our outside scientific advisors -- either new programs or expansions of ongoing programs -- that we will not be able to pursue at the proposed FY 1991 funding level for the Institute.

Mr. Early. Please provide, for the record, a list of these along with a brief description and the funding requirements associated with each.

Dr. Gorden. There are a number of areas and opportunities for increased support. They are as follows:

Research Initiative	Estimated Cost FY 1991 Dollars in Thousands
Fully fund all research project grants	$ 51,000
Fully fund all centers	15,000
Fund to 45th percentile in all divisions	90,000
Obesity Prevention Initiative	4,000
Establish 15 new centers (including Diabetes Interdisciplinary Research Centers, Obesity Centers, Clinical Nutrition Research Centers, Inflammatory Bowel Disease Centers, George O'Brien Kidney and Urologic Disease Research Centers, Digestive Disease Centers, Centers in Pediatric Pancreatic Problems)	15,000
Initiate eighteen new clinical trials as below	25,250

Titles of Proposed Trials

- Diet and Exercise in the Prevention and Treatment of Noninsulin-dependent Diabetes Mellitus
- Clinical Study of Gallstone Recurrence Following Extracorporeal Shock-Wave Lithotripsy
- Use of Recombinant Human Erythropoietin in Adult and Pediatric Patients with Renal Failure
- Clinical Trials in the Treatment of Primary Biliary Cirrhosis
- Comparison of Therapeutic Modalitites in the Treatment of Interstitial Cystitis
- Comparison of Surgery Versus Medical follow-Up in Asymptomatic Hyperparathyroidism
- Clinical Trial of Prevention and Therapy of Hypertensive Renal Disease in Blacks
- Enzyme Replacement Therapy in Inherited metabolic Diseases
- Immunosuppressants in Crohn's Disease
- Effective Weight Loss Strategies for Obese Diabetics in High Risk Minority Populations
- Liver Transplantation Trials Using Alpha Interferon, PGE-1 in Severe Viral Hepatitis; Monoclonal Antibodies to Prevent Reinfection in Hepatitis; and Salmon Calcitonin After Liver Transplantation in Primary Biliary Cirrhosis Patients
- The Efficacy of Alternative Therapies for the Treatment of Symptomatic Benign Prostatic Hyperplasia
- Peptic Ulcers: Role of Helicobacter Pylori
- The Long-Term Effects of Extracorporeal Shock-Wave Lithotripsy on the Kidney and Other Organs
- Immunotherapy for Pre-Type I Diabetics
- Comparison of Amino Acid and Ketoacid Analogues to Essential Amino Acids as Nutritional Supplements for Protein Restricted Diets
- Comparison of Radioiodine versus Antithyroid Drug Therapy in Grave's Disease
- Effect of Diet on Lipid Levels in Diabetic Patients

Search for the Diabetes Genes -- An ad hoc advisory committee of outside scientists recently recommended that the NIDDK undertake a broad major enhancement of our efforts to understand the genetics of diabetes. Both Type I and Type II diabetes and their complications clearly have genetic components. Finding the genes involved, determining their functions, and unravelling their complex interactions would be the goals of this expanded effort. Our current research programs have begun to address these issues, but the proposed effort would require substantially increased resources -- estimated at approximately $50 million per year.

PRIORITIES FOR 1991

Mr. Early. If an increase over your FY 91 budget request were provided, how would your use these additional funds?

Dr. Gorden. First, we would cover our current funding shortfalls that affect the viability of all our programs. We would do this by fully funding at peer-review approved levels all research project grants and existing centers.

Our second priority would be to increase our payline in all divisions. We feel that we could fund excellent scientific research all the way up to the 45th percentile.

Third, we would intensify and initiate research in a number of critical areas including: prevention of obesity, study of diseases that disproportionately affect minority populations, investigations in pediatric nephrology questions, inflammatory bowel disease research, studies to find the genes involved in diabetes and its complications, investigations of interstitial cystitis, benign prostatic hyperplasia and polycystic kidney disease, and testing of oral chelators for use in Cooley's anemia. In addition, we would initiate eighteen promising clinical trials that are unfunded at this time. These initiatives and trials have been identified by our Advisory Council, by our statutory Advisory Boards, by an array of ad hoc advisory groups, and by our internal planning process.

KIDNEY DISEASE OF DIABETES MELLITUS

Mr. Dwyer. Last year, both the House and the Senate reports contained language urging the Institute to aggressively combat diabetes-related kidney disease, the leading cause of renal failure. It is my understanding that a new request for applications has been issued in the area of diabetes mellitus. What is the status of this RFA? When will the grants be made?

Dr. Gorden. The NIDDK issued a new RFA in January, 1990, in an effort to enhance its research effort against KDDM. Although the RFA's April application deadline has not yet arrived, the Institute has heard from the research community that many investigators are planning to apply and compete for funding under this RFA. It is anticipated that the research applications generated from this RFA will be peer-reviewed and presented to the Institute's National Advisory Council by September, 1990, with funding of these grants to follow shortly thereafter.

Mr. Dwyer. How many grants does NIDDK expect to make in this area?

Dr. Gorden. The number of grants that the Institute is able to fund as a result of the RFA on kidney disease of diabetes mellitus (KDDM) issued in January 1990 will depend on the scientific merit of the research of the applications received. We would hope to fund 10-15 such grants, at a minimum, provided that they are of high scientific quality. In addition, the Institute funded nine grants earlier in FY 1990 for research on KDDM under a previously issued RFA.

UNDIAGNOSED DIABETICS

Mr. Dwyer. Your budget justification states that there are 11 million diabetics in this country, but half of them remain undiagnosed. What education initiatives are under way to make these individuals aware that they are diabetics and to seek the proper treatment for this disease?

Dr. Gorden. The great majority of the undiagnosed diabetics in this country suffer from noninsulin-dependent diabetes. This disease tends to appear very gradually in later life, and be preceded by years of impaired glucose tolerance and obesity. The hope is that if these individuals who are at risk for developing diabetes could be identified early, then improved diet, weight control, and exercise might delay or prevent onset of the disease or its complications.

Our aim generally has been to educate health professionals, so that they are alert to the presence of risk factors in their patients. We support an important effort, the National Diabetes Information Clearinghouse, that serves as a resource regarding the existence and location of a number of educational materials about diabetes that are useful to health professionals and to the general public. The organization provides a national focus for information collection and distribution relating to diabetes. Included among the publications of the Clearinghouse are a bibliography of Spanish language materials and a newsletter. A new resource guide concerning diabetes in the Black population is currently being developed.

In addition, the NIDDK supports six Diabetes Research and Training Centers. The legislative mandate for these centers states that each center will conduct "training programs for physicians and allied health personnel in current methods of diagnosis and treatment" of diabetes, and "information programs for physicians and allied health personnel who provide primary care for patients." These centers also have model demonstration units to help develop outreach projects that can then be implemented by the appropriate health care delivery organizations. This work has been especially important for programs relating to minority populations. For instance, at the Albert Einstein Diabetes Research and Training Center, the screening process used by health care professionals for individuals with Type II diabetes is being evaluated. In addition, studies at other centers are investigating possible programs for weight control and lifestyle modification.

An important aspect of diabetes education is cooperative interaction between the NIDDK and private sector organizations such as the American Diabetes Association and the Juvenile Diabetes Foundation. These groups conduct active campaigns to increase public awareness and understanding of the symptoms and complications of diabetes.

DIABETES IN MINORITIES

Mr. Dwyer. Your budget justification mentions the high numbers of minorities which suffer from the disease. Can we conclude that a large percentage of those undiagnosed individuals are minority?

Dr. Gorden. Most minority groups have a higher prevalence of diabetes than Whites. For example, in Blacks the prevalence is over one and a half times as high, while Hispanics have almost a two fold higher prevalence than Whites.

During 1976-80, the National Health and Nutrition Examination Survey studied the presence of undiagnosed diabetes in a sample of persons with no medical history of diabetes. The rates of undiagnosed diabetes in the 20-74 year age group that the study examined were compared for Blacks and Whites. The conclusion was that undiagnosed diabetes occurred at a rate about equal to the rate of diagnosed diabetes in either Blacks or Whites.

To restate this in a different way, if all cases of diabetes were diagnosed, both Blacks and Whites would show a prevalence twice as high as is reported now, but the relative prevalence of the disease in Blacks as compared to Whites would be expected to be the same -- about one and a half times the rate.

Mr. Dwyer. What initiatives are currently underway to reach minority populations?

Dr. Gordon. A major function of the Diabetes Research and Training Centers (DRTC) is to conduct information and training programs for physicians and allied health personnel in current methods of diagnosis and treatment of diabetes. At several DRTCs, a particular focus has been on pilot studies of various aspects of diabetes in minorities.

The University of Chicago DRTC is working on a program to help an obese minority population make lifestyle changes. Most of these individuals are Blacks with Type II, noninsulin-dependent diabetes (NIDDM). Such a program would help these patients to achieve weight loss and metabolic control.

At the Vanderbilt DRTC a study is trying to understand eating patterns in a Black obese population. Again, the ability to modify diet would affect diabetes control in this group. The results may prove valuable in minority diabetes education.

Examination of the screening process used at federally-funded urban primary care clinics is underway at the Albert Einstein DRTC in the Bronx, New York. Results to date have already shown that better assessment of risk factors for the vascular complications of diabetes is needed in this setting, as well as nutrition information that could lead to weight control.

Research project grants supported by the Institute also address diabetes in minorities. Studies on topics such as the epidemiology of diabetic complications or obesity in Black women may prove helpful in identification and treatment of minority diabetics.

The NIDDK's National Diabetes Information Clearinghouse distributes publications to diabetes health educators and professionals to help in presenting programs for minority diabetics.

The Institute also has sponsored and participated in several important meetings concerning diabetes in minorities. These included: Diabetes in the Black Population, Diabetes in Native Americans and Alaska Natives, and Diabetes in Hispanics. These meetings have served to focus and intensify efforts to understand diabetes as it occurs in minority populations. Recently, the NIDDK and the Indian Health Service signed a Memorandum of Understanding to facilitate improvements in the diagnosis, treatment, cure, and prevention of diabetes and its complications in American Indians and Alaska Natives through research in this area.

GENETICALLY ENGINEERED INSULIN

Mr. Dwyer. Insulin-dependent diabetics now can use genetically-derived insulin versus animal-derived. Is genetically-derived insulin available worldwide and what efforts are underway to expand its availability?

Dr. Gorden. Several pharmaceutical companies are involved in the production and sale of genetically engineered insulin. To my knowledge, these products are widely available throughout the world.

INSULIN PUMPS

Mr. Dwyer. NIDDK is working to develop an effective insulin pump. Generally these pumps are preprogrammed to dispense insulin at some sort of regular interval. It would appear that this type of pump could not be effectively used by those diabetics who have difficulty controlling their diabetes. Is this true?

Dr. Gorden. The NIDDK continues to support a number of research projects related to improved mechanical devices for the delivery of insulin. At this time, however, all of these devices rely on the user for control of the timing and amount of dosage. This means that the control of blood sugar that results is still totally dependent on the ability of the patient and her/his health care providers to make appropriate decisions. Unfortunately we are just not as smart or quick as the natural pancreatic beta cell which, on a minute-to-minute basis, senses the blood sugar and makes precise adjustments of insulin delivery. Therefore, the pump is not a perfect solution, especially in those patients who inherently have a volatile blood sugar level.

Mr. Dwyer. When do you believe that sensor equipped pumps will become available?

Dr. Gorden. The NIDDK is actively supporting the development of an automatic, continuous, and accurate glucose sensor which could "close the loop" for the automatic feedback control of an insulin pump in a way that more closely approximates the way natural pancreatic beta cells work. This goal presents a number of significant technological challenges that have yet to be met. We remain encouraged by the progress made in the last few years and the participation of the private, corporate sector (partially supported through our Small Business Innovation Research Program) along with the academic research community in this endeavor. It is impossible to accurately guess when success will occur, but I believe we have several years of fairly basic research ahead of us before a clinically acceptable sensor is available.

COMPLICATIONS OF DIABETES

Mr. Dwyer. A number of serious complications can result from both insulin- and noninsulin-dependent diabetes. Do certain complications occur more frequently in one type of diabetes versus another?

Dr. Gorden. Recent research has documented that complications of the eyes and kidneys occur more frequently in persons with insulin-dependent (Type I) diabetes compared to persons with noninsulin-dependent (Type II) diabetes. Diabetic retinopathy leading to visual loss and eventual blindness is about 6 times greater among persons with Type I than Type II diabetes. The risk of end-stage renal disease, leading to treatment through Medicare, is about 12-fold higher. This may be explained to some degree by the fact that patients with IDDM generally become ill at a younger age and have a longer life ahead of them during which these complications may become evident. However, it should be remembered that persons with Type II diabetes constitute 90 percent of the total diabetic population in the United States. Hence the burden represented by the two types of diabetes is rather similar.

Mr. Dwyer. Are diabetic complications approached and treated differently in insulin- and noninsulin-dependent diabetics?

Dr. Gorden. The long-term complications of diabetes appear to be caused by the same underlying pathological processes regardless of the type of diabetes. Therefore, the approaches and treatments are similar for all diabetics. However, it is relevant to point out that, in general, patients with insulin-dependent diabetes (IDDM) are young while those with noninsulin-dependent diabetes (NIDDM) tend to be in late middle age or older. As would be true with many clinical situations, approaches to a chronic potentially debilitating problem would be tempered by the inherent age and life expectancy of the patient. For example, the aggressiveness of preventative interventions to minimize the chances of blindness or kidney failure which may occur in 10 or 20 years is likely quite different for a patient who develops IDDM at age 15 than for a patient who develops NIDDM at age 65.

Mr. Dwyer. How many individuals are treated for these complications but are not diagnosed as being diabetic?

Dr. Gorden. Our studies have shown that about 5.5 million adults in the United States have diabetes but do not know it. Noninsulin-dependent diabetes can be insidious and present only vague symptoms that are not recognized. None of these individuals are being treated for their diabetes. This is particularly devastating because the frequency and impact of diseases of the eyes, kidneys, nerves, and heart are much more severe in persons with diabetes compared to those without the disease, and more intensive medical care is called for when a person has diabetes. Unfortunately, many people are diagnosed as having diabetes only when these complications develop. Patients can present with visual loss, a heart attack, nerve damage or a nonhealing skin ulcer suggesting diabetes which is then confirmed by testing and probably existed for many years. We know for example, that about 15 percent of diabetics have evidence of diabetic retinopathy at diagnosis. Undoubtedly, this is due to onset of diabetes years earlier.

OSTEOPOROSIS

Mr. Dwyer. Much publicity has been given to the disease osteoporosis, which accounts for nearly 1.3 million fractures each year. Calcium pills, increased exercise and estrogen therapy have all been touted as effective treatments or preventative therapies for osteoporosis. Do any of them work?

Dr. Gorden. Strategies for preventing osteoporosis are clearly more effective than those for treating the established disease. Peak bone mass or the amount of bone present at maturity is now recognized as a key determinant of osteoporosis later in life. We know that the amount of bone present at maturity is largely determined by heredity, but diet and exercise can influence whether or not full genetic potential is achieved. For these reasons, current preventive efforts focus on maintaining adequate calcium intake and exercise during adolescent and early adult life. The Recommended Dietary Allowance (RDA) for calcium for women 12-24 years of age was recently increased to 1,200 milligrams per day in order to reduce the risk of developing osteoporosis in later life. Regular exercise in young adult women involving skeletal stress from weight bearing and muscle contraction has been shown to be an effective method of presenting bone loss in many cases to increase bone mass.

With respect to the prevention of osteoporosis in post-menopausal women, to date estrogen replacement therapy in conjunction with an adequate calcium intake is the most effective strategy for slowing the rapid rate of bone loss that may occur early in the post-menopausal period. Estrogen replacement therapy has the added benefit of reducing menopausal symptoms as well as possibly decreasing the risk of cardiovascular disease. However, concerns have been raised about the effect of estrogen on breast and other estrogen-dependent cancers.

Once osteoporosis has developed, exercise, estrogen and calcium may delay the rate of progression. Unfortunately, efficacy in restoring lost bone mass has been difficult to achieve with these or other agents.

Mr. Dwyer. What other therapies are currently being investigated which would increase bone density?

Dr. Gorden. Therapeutic agents currently being investigated which would increase bone density are those directed at modulating bone resorption and deposition. These are calcitonin, sodium fluoride, the biophosphonates such as etidronate, parathyroid hormone and vitamin D analogues. Recent results with fluoride therapy were disappointing--although bone density improved, the risk of bone fracture did not. Thus, the improved density of bone achieved with this agent does not appear to reflect increased strength of bone. This suggests that the finding that any agent increases bone density must be interpreted cautiously. Effective therapy of osteoporosis requires reduction of the fracture rate as well as radiographic improvement.

Strategies for treatment now being evaluated are based on knowledge of bone physiology. Agents are being investigated for the most part in combination in a form of treatment known as coherent therapy or ADFR (activation, depression, free period, retreatment). This treatment involves first the activation of the bone resorbing cells, the osteoclasts. This function is subsequently depressed, thus allowing the osteoblasts or bone-forming cells to function. Theoretically, this form of therapy would not only prevent further loss, but also result in the restoration of bone.

CYSTIC FIBROSIS TESTING

Mr. Dwyer. A recent article in the Washington Post contended that testing for cystic fibrosis is not precise enough. Since the discovery of the gene linked to cystic fibrosis, what efforts have been undertaken to improve the testing of at-risk individuals?

Dr. Gorden. NIDDK and other components of the NIH recently convened a workshop to address issues related to population screening for cystic fibrosis. The panel members concluded that testing is feasible in individuals at risk by virtue of having a family member with the disease. Unlike testing in the general population, carrier testing in families in which the disease has occurred is nearly 100 percent informative. Therefore, carrier testing should be offered to all individuals and/or couples with a family history of cystic fibrosis.

The problem referred to in the Washington Post applies to screening the general population for the cystic fibrosis gene. Since the discovery of the gene linked to cystic fibrosis, scientists have found the mutation present in 70-75 percent of Caucasian carriers. A number of other rare mutations have been found, but we are not yet at the point where testing can detect 90-95 percent of carriers. Researchers are actively searching for additional mutations responsible for cystic fibrosis. Identification of other mutations is important not only for genetic testing but also for understanding the pathophysiology of the disease.

Mr. Dwyer. Is a large screening program planned to test individuals for cystic fibrosis?

Dr. Gorden. Currently, DNA analysis can identify a single mutation in the cystic fibrosis gene which is present in 70-75 percent of Caucasian carriers. Many additional mutations (currently about twenty) producing cystic fibrosis have been identified. The identification of multiple, individually rare mutations rather than a small number of common mutations will make carrier testing more difficult. The inability to detect all carriers creates complexities for the use of carrier testing at this time.

These difficulties would be substantially reduced if testing could detect at least 90 to 95 percent of carriers. There is a consensus that population screening for carriers could be offered to all reproductive-age individuals, if a 95 percent level of carrier detection were achieved.

A screening program would also require adequate resources for education and counseling. Given the problems encountered in the past in screening programs for other disorders, pilot projects should be undertaken before initiation of widespread screening programs.

DRG STUDY SECTION

Mr. Porter. Last year, the Committee asked the NIH to examine the need to develop a study section on urology. Can you provide a status report on the activities of the Institute to develop such a urology study section?

Dr. Gorden. The Division of Research Grants has the responsibility of frequently updating and revising the register of experts who perform the peer review of research grant proposals, and for establishing new study sections. The DRG is aware of the need to address all areas of medical science, and is working to ensure that all disciplines are represented appropriately. The NIDDK has brought the National Kidney and Urologic Disease Advisory Board's concerns on this issue to the DRG's attention.

PROSTATIC DISEASE

Mr. Porter. Prostate disease, both benign and malignant, affects many elderly men and causes significant health and social costs. Can you describe efforts underway now, and planned for the future, to fund basic research on the prostate?

Dr. Gorden. NIDDK has primary responsibility within the National Institutes of Health for investigating the basic science and clinical aspects of prostate disease. One of the major initiatives designated in its FY 1990 implementation plan is the development of a research plan for the investigation of the normal and abnormal growth of the prostate. Included in this plan is the issuance of program announcements to elicite research grant applications and the development of a conference to discuss the status of current research on prostate diseases, evaluate the current therapies for prostate diseases and determine areas for future research development, especially in the study of abnormal prostate growth. Studies that are now currently being supported by the NIDDK are investigating the role of specific factors, such as, hormones and growth factors which influence the normal and abnormal growth of the prostate. Other studies are being conducted to determine the conditions present in both childhood and early adulthood, which initiate this abnormal growth pattern.

Mr. Porter. Do you see value in establishing an early intervention strategy for prostatic diseases?

Dr. Gorden. Prostate diseases manifest their symptoms and thus effect health care expenditures mainly in the aging male. However, it is known that the abnormal growth and changes in the prostate are initiated in early adulthood. It is our opinion that both the morbidity and health care expense of these diseases can be markedly reduced if a greater understanding of the initiating events and early development of these diseases is acquired. This information would allow intervention for disease prevention at a younger age and thus significantly reduce the amount of health care problems in the elderly, which occur as a result of these diseases. The NIDDK is supporting research into the role of specific factors that influence the normal and abnormal growth and enlargement of the prostate. Other areas of research are being pursued, which will help to determine the conditions necessary in both childhood and early adulthood for the initiation of these abnormal prostate growth patterns.

BLADDER DISEASE

Mr. Porter. How much is the NIDDK spending in FY90 on basic bladder research? How much will you spend under the budget estimate in FY91?

Dr. Gorden. For FY 1990 the NIDDK is supporting basic bladder research at the level of approximately $2.2 million. The Institute's FY 1991 budget estimate for research in this area is $2.3 million. In addition to basic bladder research, the Institute's urology program supports applied bladder research, and basic and applied research in the areas of prostate growth, sexual function, urolithiasis, urinary tract infections, and pediatric urology.

Mr. Porter. Would increased biomedical research into basic bladder function yield progress in the fight against urinary incontinence?

Dr. Gorden. Increased biomedical research into basic bladder function is essential if significant progress is to be made in the fight against urinary incontinence and other significant disorders of the bladder including urinary tract infections, interstitial cystitis and the effect on the bladder of prostate diseases such as benign prostatic hyperplasia. The development of research centers of excellence to study basic bladder function would be an effective way to coordinate research on basic bladder function with research on effective methods of treatment of diseases of bladder function such as urinary incontinence. The augmentation of research in this area is one of our highest priorities and will require the development of many new investigators in urologic diseases.

Mr. Porter. The National Kidney and Urologic Diseases Advisory Board has pointed with concern to the need to develop an expanded program aimed at women's urologic diseases--especially in the areas of urinary incontinence, urinary tract infection, and interstitial cystitis. Can you describe for the record the NIDDKs current and future planned activities in this area?

Dr. Gorden. The National Institute of Diabetes and Digestive and Kidney Diseases has primary responsibility within the National Institutes of Health for developing the research program aimed at women's urologic diseases. A 5-year plan for research into interstitial cystitis has been developed and is now in its second year of progress. Long-range plans for research programs into the other bladder disorders are also being developed. These plans will include specific program initiatives such as program announcements, conferences, and workshops to focus and stimulate research in these areas. If funds designated for specific research areas become available, requests for applications will be issued to ensure funding of the maximum number possible of research grant applications in a specific area. An essential part of all these initiatives is the development of a cadre of outstanding investigators in the basic science aspects of these disorders. The research community has repeatedly expressed its concerns to the NIDDK about the development of this group of young investigators in the face of the restricted budget available for funding grant applications. Realizing these concerns, the NIDDK seeks to fund those applications that have been accorded the highest scientific merit rating from the peer review system.

Mr. Porter. Has NIDDK considered the establishment of a new, multi-site O'Brien center focused on women's urological health problems, especially interstitial cystitis?

Dr. Gorden. Within existing resource levels, the NIDDK cannot establish additional George O'Brien Kidney and Urologic Research Centers. We currently have six such centers and their research agendas are relatively broad, consistent with the research goals originally set out for this program by the Congress. The specific research agenda of each individual center was independently determined by the investigator at the time the application was submitted, consistent with the research team's scientific interests and expertise.

Although the research focus of each center is relatively well established, the NIDDK has considered ways in which emerging research issues of particular concern -- such as interstitial cystitis and pediatric nephrology -- might be incorporated within our existing program of six George O'Brien Kidney and Urologic Diseases Centers. In this regard, I am pleased to report that, very recently, we were able to award a supplemental grant to the existing O'Brien urology center at Northwestern University Medical Scool for the establishment of a pilot data base on interstitial cystitis. We are hopeful that this data base, which will test the validity of the newly established diagnostic criteria in IC patients, may also provide patient volunteers for possible future clinical studies and trials.

In Fiscal Year 1991, the original six O'Brien center grants will expire, and we will be entertaining research grant applications for the O'Brien centers program from potential new applicants, as well as from existing centers who may wish to compete for a grant renewal. When we issue the solicitation for O'Brien center grant applications in Fiscal Year 1991, we will certainly encourage applicants to include activities that address research areas of special concern, such as interstitial cystitis.

UROLOGICAL CANCERS

Mr. Porter. Provide for the record a summary of NIDDK activity in the area of urological cancers. Do you coordinate these efforts with the NCI?

Dr. Gorden. The NIDDK supports research activities in the basic science of normal and abnormal cell growth regulation in all of the urological organ systems including the bladder, prostate and kidney. In cases where this basic research is conducted on both cancer and non-cancer tissue, the grant application receives dual assignment to both the National Cancer Institute and the NIDDK. Funding of these grants is determined by advisory councils' actions based on the recommendations from the program directors in both of the institutes. In many instances, the primary investigator will receive funding from both institutes by submitting separate grant applications applicable to the research program of each institute. Examples of these research areas are the studies of the effects of growth factors on cell growth, modulation of the immune properties of certain tissues, the effect of various tissue elements on the control of other cell growth and the effect of various natural and synthetic products on the regulation of normal and abnormal cell growth.

FETAL TISSUE

Mr. Porter. Last year Dr. Wyngaarden discussed with this committee research on diabetes that relies heavily on the use of pancreatic fetal tissue. Please describe this research.

Dr. Gorden. One area of research on insulin dependent diabetes is the use of fetal pancreatic cell transplants in an attempt to replace pancreatic islet cells that have been destroyed by diabetes. For this purpose, fetal pancreatic tissue is non-immunogenic and has the potential to grow and to differentiate. Since March 1988, the Department has had a moratorium on all research projects which involve the implantation into human subjects of human fetal tissue obtained from induced abortions. This moratorium does not affect research supported by the private sector.

Mr. Porter. What is NIH policy regarding the use of human fetal tissue?

Dr. Gorden. The NIH policy is consistent with the Department's current policy, that is, a moratorium on Departmental funding of research in which human fetal tissue from induced abortions is transplanted into human recipients. On November 2, 1989, Secretary Sullivan informed the Acting NIH Director, Dr. Raub, of his decision to continue indefinitely this moratorium. Accordingly, on November 3, 1989, Dr. Raub directed the NIH community to implement this decision and to inform both intramural and extramural researchers of the policy. The moratorium does not limit the use of human fetal tissue for research other than transplantation into human recipients.

Mr. Porter. Has this policy inhibited research that could otherwise have been undertaken?

Dr. Gorden. The moratorium does not apply to research funded outside of the Department, and investigators who choose to pursue this avenue of research with private funds may do so. At the time the moratorium was imposed, there were only two NIH projects affected, one planned and one ongoing. In the case of the latter, the investigator voluntarily stopped the project. We do not know whether other research applications in this area would have been submitted to the NIH for possible funding if the moratorium were not in effect.

Mr. Porter. In your professional judgment, should the policy on scientific use of fetal tissue be modified? If so, how?

Dr. Gorden. This is a complex public policy question with respect to the appropriateness of Federal support for this type of research, and one which requires broad-based consideration and judgment.

In 1988, the NIH convened a very distinguished panel of individuals from a wide array of backgrounds -- the Human Fetal Tissue Transplantation Research Panel. After several meetings, this group eventually concluded that it is acceptable public policy to conduct Federally-funded research involving therapeutic transplantation of human fetal tissue, although there were strongly opposing minority opinions. The Advisory Committee to the Director, NIH, endorsed the Panel's report, and the NIH Director requested that the moratorium be lifted and that the NIH be allowed to develop guidelines in accordance with the safeguards recommended by the Human Fetal Tissue Transplantation Research Panel.

After careful consideration of these recommendations and other factors, the Secretary for Health and Human Services concluded in November, 1989, that a decision to lift the moratorium would be inconsistent with Administration policy and Congressional directives.

Mr. Porter. Have you been able to develop substitutes for pancreatic fetal tissue? If so, how effective are they?

Dr. Gorden. For the kind of transplantation research we have been discussing, the nearest thing to pancreatic fetal islet tissue is the corresponding adult tissue. The Institute is supporting human and animal research on ways to allow transplanted adult pancreatic islet cells to survive and function, either by modifying the cells in the transplant or by altering the recipient's immune response. At this point, however, adult islet cell transplants have not survived in the recipient for extended periods of time.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

FY 1991 Budget — Page No.

Appropriation language and explanation of language changes......... 2

Amounts available for obligation.................................... 3

Budget mechanism table.. 4

Crosswalk tables.. 6

Summary of changes.. 9

Budget authority by activity.. 10

Budget authority by object.. 11

Significant items in House and Senate Appropriations Committee reports.. 13

Authorizing legislation... 17

Appropriations history... 18

Justification:

A. General statement.. 19
B. Program accomplishments.. 21
C. AIDS research program.. 31
D. Diabetes, endocrinology and metabolism......................... 34
E. Digestive diseases and nutrition............................... 42
F. Kidney disease, urology and hematology......................... 49
G. Intramural research.. 55
H. Research management and support................................ 64
I. Detail of permanent positions.................................. 65
J. Advisory and assistance services............................... 67

2

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to diabetes and digestive and kidney diseases. [$591,887,000] *$605,349,000.*

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1990.)

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation................	$567,158,000	$591,887,000	$605,349,000
Enacted administrative reduction..................	-7,620,000	-2,293,000	---
Sequestration................	---	-8,117,000	---
Subtotal, adjusted appropriation............	559,538,000	581,477,000	605,349,000
Real transfer to the Office of the Assistant Secretary for AIDS research for AZT..	-44,000	---	---
Comparative transfers to:			
Division of Research Resources, NIH, for RCMI grant administration.......	-18,000	---	---
Fogarty International Center, NIH, to administer passport activities........	-11,000	-11,000	---
Comparative transfer from:			
Office of the Director, NIH for full-time equivalent positions..................	421,000	---	---
Subtotal, adjusted budget authority.......	559,886,000	581,466,000	605,349,000
Unobligated balance lapsing..	-220,000	---	---
Total, obligations.........	559,666,000	581,466,000	605,349,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1989 -- $2,974,000; 1990 -- $4,972,000; 1991 -- $5,000,000.

Note: Excludes $13,000 for royalties received in 1989.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Mechanism
(Dollars in thousands)

	1989 Actual		1990 1/ Appropriation		1991 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects						
Noncompeting	1569	297,154	1607	317,990	1534	317,573
Administrative supplementals	(48)	1,936	(40)	1,322	(40)	1,385
Competing						
Renewal	243	54,498	202	48,630	239	60,410
New	255	37,640	213	33,615	251	41,854
Supplemental	6	317	5	300	5	300
Subtotal, competing	504	92,455	420	82,545	495	102,564
Subtotal, research projects	2073	391,545	2027	401,857	2029	421,522
Research centers						
Specialized/Comprehensive centers	40	34,185	40	33,766	40	33,766
Other research						
Research career programs	153	10,513	178	12,211	178	12,211
Cooperative clinical research						
Minority biomedical research support		1,447		1,462		1,586
Other research related	86	3,080	60	3,464	60	3,464
Subtotal, other research	239	15,040	238	17,137	238	17,261
Total, research grants	2,352	440,770	2,305	452,760	2307	472,549

Training						
Individual awards:						
Noncompeting	57	1,689	118	3,040	120	3,082
Competing						
Renewal						
New	73	2,118	60	1,462	58	1,420
Subtotal, individual	130	3,807	178	4,502	178	4,502
Institutional awards						
Noncompeting	590	15,455	575	15,524	597	16,128
Competing						
Renewal	91	2,317	110	2,972	100	2,702
New	14	370	32	864	20	540
Subtotal, institutional	695	18,142	717	19,370	717	19,370
Total, training	825	21,949	895	23,872	895	23,872
Research and development contracts	44	13,047	52	14,935	52	14,935
	FTEs		FTEs		FTEs	
Intramural research	435	64,240	428	68,728	439	73,295
Research management and support	162	19,880	175	19,916	179	20,698
Extramural construction		---		1,255		---
Total	597	559,886	603	581,466	618	605,349
HIV/AIDS	(10)	(3,676)	(10)	(5,320)	(10)	(5,791)

1/ Includes approximately $1,255,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

CROSSWALK - 1989 Actual
(Dollars in thousands)

PROGRAM ACTIVITY	Mechanism: Research Grants: Research Projects	Research Centers	Other Research	Training Programs: Individual	Institutional	R & D Contracts	Intramural Research	Research Management & Support	Total
Diabetes, Endocrinology and Metabolism.....	$194,899	$18,468	$9,548	$1,948	$8,193	$9,685			$242,741
Digestive Diseases and Nutrition......	94,203	11,517	2,481	936	4,981	933			115,051
Kidney Disease, Urology and Hematology.....	102,443	4,200	3,011	923	4,968	2,429			117,974
Intramural Research.......							$64,240		64,240
Research Management and Support....								$19,880	19,880
Total...........	391,545	34,185	15,040	3,807	18,142	13,047	64,240	19,880	559,886

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

CROSSWALK - 1990 Appropriation[1/]
(Dollars in thousands)

PROGRAM ACTIVITY	Mechanism								
	Research Grants			Training Programs					
	Research Projects	Research Centers	Other Research	Individual	Institutional	R & D Contracts	Intramural Research	Research Management & Support	Total
Diabetes, Endocrinology and Metabolism.....	$199,857	$17,981	$11,224	$2,080	$8,950	$9,835			$249,927
Digestive Diseases and Nutrition......	95,700	11,690	3,095	1,214	5,221	2,250			119,170
Kidney Disease, Urology and Hematology.....	106,300	4,095	2,818	1,208	5,199	2,850			122,470
Intramural Research.......							$68,728		68,728
Research Management and Support....								$19,916	19,916
Extramural Construction...	1,255								1,255
Total...........	403,112	33,766	17,137	4,502	19,370	14,935	68,728	19,916	581,466

[1/] Includes approximately $1,255,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

CROSSWALK - 1991 Estimate
(Dollars in thousands)

PROGRAM ACTIVITY	Mechanism: Research Grants: Research Projects	Research Grants: Research Centers	Research Grants: Other Research	Training Programs: Individual	Training Programs: Institutional	R & D Contracts	Intramural Research	Research Management & Support	Total
Diabetes, Endocrinology and Metabolism.....	$209,899	$17,981	$11,348	$2,080	$8,950	$9,835			$260,093
Digestive Diseases and Nutrition......	100,446	11,690	3,095	1,214	5,221	2,250			123,916
Kidney Disease, Urology and Hematology.....	111,177	4,095	2,818	1,208	5,199	2,850			127,347
Intramural Research.......							$73,295		73,295
Research Management and Support....								$20,698	20,698
Total...........	421,522	33,766	17,261	4,502	19,370	14,935	73,295	20,698	605,349

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Summary of Changes

1990 Estimated budget authority	$581,466,000
1991 Estimated budget authority	605,349,000
Net Change	+23,883,000

Changes:	1990 Current Estimate Base Pos. (FTEs)	1990 Current Estimate Base Budget Authority	Change from Base Pos. (FTEs)	Change from Base Budget Authority
A. Built-in:				
1. Annualization of 1990 pay raise		$33,882,000		+$452,000
2. Within-grade increases		33,882,000		+647,000
3. 1991 pay raise		33,882,000		+1,366,000
4. One extra day of pay		33,882,000		+135,000
5. Federal Employees Compensation Fund		104,000		+3,000
6. Unemployment compensation		49,000		+2,000
7. FTS rate increase		478,000		+16,000
8. DHHS Working Capital Fund		677,000		+31,000
9. Increased cost of centrally furnished services		24,092,000		+994,000
10. Increased cost of service and supply fund		15,836,000		+42,000
11. Increased cost of supplies and materials		30,670,000		+1,293,000
Subtotal				+4,981,000
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	1607	319,312,000	-73	-354,000
b. Competing	420	82,545,000	+75	+20,019,000
Total	2027	401,857,000	+2	+19,665,000
2. Other research	238	17,137,000	--	+124,000
3. Extramural construction		1,255,000		-1,255,000
4. Intramural research	(FTEs) (428)	68,728,000	(+11)	+239,000
5. Research management and support	(175)	19,916,000	(+4)	+129,000
Subtotal				+18,902,000
Total changes				+23,883,000

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Activity
(Dollars in thousands)

	1989 Actual		1990 1/ Appropriation		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Diabetes, endocrinology and metabolism.............		$242,679		$249,927		$260,093
Digestive diseases and nutrition..................		115,051		119,170		123,916
Kidney disease, urology and hematology.............		117,974		122,470		127,347
Intramural research..........	435	64,082	428	68,728	439	73,295
Research management and support................	162	19,880	175	19,916	179	20,698
Extramural construction......		---		1,255		---
Subtotal, obligations......	597	559,666	603	581,466	618	605,349
Unobligated Balance Lapsing....................		+220		---		---
Total, Budget authority....		559,886		581,466		605,349
HIV/AIDS................	(10)	(3,676)	(10)	(5,320)	(10)	(5,791)

1/ Includes approximately $1,255,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Total number of full-time permanent positions.................	416	431	+15
Total compensable workyears:			
Full-time equivalent employment.....	611	626	+15
Full-time equivalent of overtime and holiday hours.................	7	7	---
Average ES salary.....................	$78,267	$95,333	+$17,066
Average GM/GS grade..................	10.4	10.3	-0.1
Average GM/GS salary..................	$37,325	$38,669	+$1,344
Average salary, grades est. by act of July 1, 1944 (42 USC 207)...........	$71,400	$73,970	+$2,570
Average salary of ungraded positions..	$19,091	$19,779	+$688
Personnel compensation:			
Permanent positions.................	$16,575	$17,920	+$1,345
Positions other than permanent......	7,841	8,335	$494
Other personnel compensation........	1,159	1,240	+81
Special personnel services..........	3,212	3,389	+177
Subtotal, personnel compensation..	28,787	30,884	+2,097
Personnel benefits....................	5,095	5,467	+372
Benefits for former personnel.........	19	20	+1
Travel and transportation of persons..	1,005	1,060	+55

12

Budget Authority by Object - cont'd

	1990 Appropriation	1991 Estimate	Increase or Decrease
Transportation of things..............	159	165	+6
Rent, communications and utilities....	1,605	1,690	+85
Printing and reproduction.............	273	285	+12
Other services:			
Project contracts....................	14,935	14,935	---
Centrally furnished services........	23,388	24,573	+1,185
Standard level user charge.........	704	513	-191
Other................................	15,836	17,789	+1,953
Supplies and materials................	8,692	9,126	+434
Equipment.............................	4,335	2,420	-1,915
Grants, subsidies and contributions...	476,632	496,421	+19,789
Interest and dividends................	1	1	---
Total......................	581,466	605,349	+23,883

National Institute of Diabetes and Digestive and Kidney Diseases

Significant Items in House and Senate Appropriations Committee Reports

Item	Action taken or to be taken
1990 House Report	
1. "The Committee is aware that diabetes-related kidney disease is the leading cause of renal failure and is on the rise in the United States. . . . The Medicare-supported End Stage Renal Disease program--which presently costs the federal government $3 billion annually--currently treats 130,000 patients, about 40,000 of whom are on dialysis because of diabetes. . . .The Committee considers research in this important area to be of the highest priority and has provided increased funds to the Institute for meritorious projects in this field." (page 59).	1. A new request for application has been issued in the area of the Kidney Disease of Diabetes Mellitus which is expected to significantly increase the basic and applied research efforts to combat kidney disease and the need for dialysis.
2. "The Committee remains supportive of the Digestive Disease Centers program, which provides a network of research expertise involving basic and clinical investigators in joint efforts to address the causes, diagnosis, prevention, and treatment of digestive diseases and nutritional disorders." (page 60).	2. Support of digestive disease centers will be continued in 1991 at the same levels as in 1990.
3. "The Committee urges the Institute to consider the establishment of training programs for researchers within the George O'Brien Kidney and Urology Centers." (page 61).	3. NIDDK has reviewed the status of the center grants and at this time it would be inappropriate to include a research training component, as this activity has not received peer review. NIDDK staff will reassess the impact of including a training component before the next announcement for new or competing renal applications.

Item	Action taken or to be taken
1990 House Report continued	
4. "The Committee has heard testimony about serious training problems in the area of pediatric nephrology and urges the Institute to address this problem." (page 61).	4. The Institute shares the concern about the shortage of pediatric nephrologists and efforts are being made to encourage more young doctors to enter careers in research.
5. "The Committee notes urology grants are currently reviewed by 19 study sections most of which do not have urologists. The Committee requests that the Director consider possible solutions to the problem." (page 61).	5. The Division of Research Grants, which is responsible for the administration of the study sections that perform the primary peer review of research grant proposals, is constantly updating and revising its lists of potential reviewers and the rosters of each study section to address the need for appropriate expertise and to ensure that all disciplines are represented.
1990 Senate Report	
1. "The Committee is pleased with the progress that NIDDK has made to date in addressing the high incidence of diabetes in the American Indian and Alaskan Native populations, and urges a continued commitment to addressing the problems of these native American peoples in cooperation with the Indian Health Service." (page 121).	1. For more than twenty-five years the NIDDK has enjoyed a cooperative and productive relationship with the Indian Health Service. Research will continue to focus on diabetes and kidney disease among the Pima Indians at our facilities in and near Phoenix, Arizona.
2. "The area of hormone regulation and hormone production is an exciting field of scientific interest which affects most important functions of the human body. Because of the intricate relationship between the endocrine system and these body functions, the Committee is pleased that the institute	2. Basic reesarch in endocrinology will receive an appropriate portion of the overall funding increase to maintain the current emphasis.

Item	Action taken or to be taken
1990 Senate Report continued	
has included basic research initiatives in this area in past years. Because of the expanding information in this area specifically as it relates to immune factors in hypo-and hyperthyroidism and the emerging roles of various proteins in endocrine regulation, the Committee directs that continued emphasis be placed on basic endocrinology research." (page 122).	
3. "The Committee is concerned about the impact of the proposed budget for the Digestive Research Centers Program. The Committee expects the Institute to give high priority to additional funding for the centers with the additional funding provided by the Committee...Additionally, the Committee is concerned about the severe shortage of young investigators entering the field of digestive disease, and the Committee is not convinced that the institute is making an effort to provide opportunities for young investigators to pursue a career studying digestive diseases. The Committee suggests that the Institute follow the recommendations of the Institute of Medicine study outlining needs for digestive disease research training." (page 122/123).	3. The increased funding provided will be used for studies focused on inflammatory bowel disease, through centers where appropriate but also through regular research project grants. It is hoped that a recent increase in stipend levels and the stability of new research career award slots will encourage more young investigators to pursue careers in digestive diseases.
4. ". . . The Committee urges effort to continue improving nonsurgical means for the prevention and treatment of kidney stone formation. A drug for the prevention of one type of renal stones has recently been approved. Scientists now have a better understanding of the role of the androgic hormones in regulating prostate growth, information that may help determine the causes and prevention of benign prostatic hyperplasia. . . . The Committee	4. Within its authorities, limited to training for careers in research, NIDDK is actively encouraging pediatric nephrologists to participate. However, we cannot support the primary training in any of the medical specialties. In regards to the Committee's concern for the lack of urologists on the study sections, the Division of

Item	Action taken or to be taken
1990 Senate Report continued	
continues to be concerned that there are serious training problems in pediatric nephrology. This matter was addressed during last year's bill and NIDDK is urged to give every consideration to making special arrangements to effectively address this matter this year. . . . The Committee has become aware that there are at least 19 NIDDK study sections which currently do not possess the expertise of urologists. The Committee recommends that the Director give serious consideration to appointing more urologists, where appropriate." (page 123).	Research Grants (DRG) has the responsibility of frequently updating and revising the register of experts who perform the peer review of research grant proposals. The DRG is aware of the need to address all areas of medical science and is working to ensure that all disciplines are represented appropriately.
5. "The Committee was pleased to receive the 5-year plan that it requested the institute to develop for research on interstitial cystitic [IC], . . . In reviewing the 5-year plan, the Committee believes the Institute has begun building a high quality and promising research program on IC. The Institute should continue working closely with the Interstitial Cystitis Association to implement the 5-year plan, which the Committee supports. The Committee further urges the NIDDK to explore the feasibility of establishing a National IC Registry and issue an RFP for such a registry within available funds." (page 123/124).	5. A pilot database is being established for the acquisition of data on patients who have been diagnosed with interstitial cystitis.
6. "The Committee is pleased to learn that nurses are an integral part of major clinical trials supported by NIDDK. These opportunities allow professional nurses to utilize their clinical knowledge and expertise to improve the quality of care delivered to patients suffering from these conditions. Therefore, the Committee strongly recommends that NIDDK continue its efforts to ensure that professional nurses are actively involved in its programs and functions." (page 124).	6. The Institute plans to continue to involve professional nurses as major new clinical trials are developed and carried out.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Authorizing Legislation

Funded Authorizations:	PHS Act/ Other Citation	U.S. Code Citation	1990 Amount Authorized	1990 Estimate	1991 Amount Authorized	1991 Budget Estimate
Research and Investigation........	Section 301	42 241	Indefinite	$557,594,000	Indefinite	$581,477,000
National Institute of Diabetes and Digestive and Kidney Diseases...	Title IV	42 285b	Indefinite		Indefinite	
Data Systems and Information Clearinghouses..................	Title IV	42 285c-1	Indefinite		Indefinite	
Division Directors................	Title IV	42 285c-2	Indefinite		Indefinite	
Interagency Coordinating Committees......................	Title IV	42 285c-3	Indefinite		Indefinite	
Advisory Boards...................	Title IV	42 285c-4	Indefinite		Indefinite	
Research and Training Centers.....	Title IV	42 285c-5	Indefinite		Indefinite	
Advisory Council Subcommittees....	Title IV	42 285c-6	Indefinite		Indefinite	
Biennial Report...................	Title IV	42 285c-7	Indefinite		Indefinite	
National Research Service Awards..	Title IV Part F	42 288	Such sums 1/ as necessary	23,872,000	Legislation 1/ to be requested	$23,872,000
Total Budget Authority....				$581,466,000		$605,349,000

1/ This training authority is shared with other research training programs of the National Institutes of Health, the Alcohol, Drug Abuse and Mental Health Administration and the Health Resources and Services Administration.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1982	$334,923,000 2/	$384,206,000	$389,663,000	368,191,000
1983	379,422,000	408,508,000	415,856,000	413,481,000
1984	426,394,000	442,255,000 3/	442,832,000 3/	460,923,000
1985	475,324,000	515,516,000 4/	545,551,000	543,576,000
1986 5/	519,858,000	541,298,000 6/	565,924,000	569,340,000
1986 Sequester				-24,482,000
1987	418,971,000	515,455,000	502,628,000	511,124,000
1988	440,504,000	563,768,000 7/	549,784,000	534,733,000
1989	562,258,000 8/	546,902,000 9/	565,908,000	559,538,000
1990	577,235,000 10/	590,276,000	593,497,000	589,594,000 11/
1990 Sequester				-8,117,000
1991	605,349,000			

1/ Reflects enacted supplementals, rescissions, reappropriations. and reductions.

2/ Reflects the September Amendment, the original request was $380,594,000.

3/ Excludes $19,135,000 in NRSA training programs not considered.

4/ Excludes $19,135,000 in NRSA training programs not considered.

5/ Amounts shown reflect the sequestered amount of $24,482,000.

6/ Excludes $26,730,000 in NRSA training programs not considered.

7/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

8/ The 1989 Request excludes funds for AIDS research and education ($3,650,000) that has been proposed for consolidation at the Office of the Assistant Secretary for Health.

9/ Exludes $25,509,000 in NRSA training programs not considered.

10/ The 1990 Request excludes funds for the National HIV program ($5,394,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

11/ Excludes enacted administrative reduction of $2,293,000.

Justification

National Institute of Diabetes and Digestive and Kidney Diseases

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
Total	603	$581,466,000	618	$605,349,000	+15	+$23,833,000
HIV/AIDS	(10)	(5,320,000)	(10)	(5,791,000)	(---)	(+471,000)

General Statement

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts and supports research on many serious diseases affecting the public health. Through basic and clinical investigation, these studies are advancing understanding of an extensive range of normal and disease states, including diabetes and other endocrine and metabolic diseases; digestive, kidney, and urologic diseases; as well as endocrinology, nutrition, and hematology. Close communication between NIDDK and other NIH programs fosters a confluence of fundamental knowledge in these vital areas of investigation.

The information exchange between basic science and clinical research is yielding a wealth of discoveries about human physiology. Research progress creates hope of treatment development for many of the debilitating and costly diseases encompassed in the research mission of NIDDK. Technologic breakthroughs in this exciting era of biomedical research affirm basic research as the foundation for treating and curing human disease.

Overall Budget Rationale

The FY 1991 budget request for the National Institute of Diabetes and Digestive and Kidney Diseases favors basic research and totals $605,349,000, an increase of $23,883,000 over the FY 1990 level. Included in the request is $5,791,000 related to AIDS research, an increase of $471,000 over the FY 1990 level.

In FY 1991, the request will support 1,534 noncompeting research project grants and 495 competing research project grants. This reflects a total increase of 2 RPGs as compared to FY 1990. An increase of 4.6 percent over the FY 1990 average costs is proposed for noncompeting research project grants. An increase of 5.4 percent over FY 1990 average costs is proposed for new and competing projects.

The FY 1991 request includes funding for 40 research centers, 178 career awards, 60 other research grants, 895 trainees, and 52 R&D contracts, the same numbers as in FY 1990.

The Intramural Research program will be conducted at $73,295,000 or $4,567,000 above the FY 1990 level. Research management and support functions will be supported at $20,698,000 or $782,000 above the FY 1990 funding level.

Program Accomplishments

Introduction

Fiscal Year 1990 is the 40th anniversary of the founding of the present National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). During this special year, the Institute is reflecting proudly on its many contributions to basic research in health and disease that have helped us to understand the complex nature of the human cell. In addition, NIDDK is proud to have achieved much in the area of clinical research to benefit those who suffer from a host of chronic diseases. To highlight the NIDDK's anniversary, this section on program achievements will emphasize advances during the history of the Institute in four specific diseases: cystic fibrosis, diabetes, end-stage liver and kidney disease. Although many other research areas could be mentioned, these four provide particularly compelling examples of how advances in basic research and animal models can lead to concrete improvements in the quality of life for millions of patients and their families.

Cystic Fibrosis

This year marks the most important discovery in cystic fibrosis (CF) research since the disease was first identified as a distinct syndrome 50 years ago. NIDDK-supported scientists have identified the gene that is defective in CF, the most common lethal genetic disease in Caucasians. Patients with CF have thick and copious mucus secretions which cause chronic and usually lethal lung and digestive disease.

In the early 1950's, NIDDK-supported scientists discovered a key metabolic abnormality in CF -- high levels of salt in sweat of patients. This finding led to a test that has been essential for diagnosis, and provided a clue to the molecular error causing the disease. After years of frustrating search for a fundamental defect that could explain all the manifestations of the disease, basic advances in cellular biology led to an NIDDK-supported researcher's breakthrough discovery in 1983 that the secretory ducts of the tissues lining CF-affected glands showed reduced permeability to chloride ions.

At the same time, monumental strides were occurring in molecular genetics, and the search for the CF gene gained momentum. New techniques in molecular biology were developed by NIDDK-supported researchers and applied directly to the search for the CF gene. Identification of the gene was crucial because, if the gene for CF were isolated, the structure of the protein it coded for could be analyzed and compared to that in CF patients. To find this gene required localizing it on one chromosome; analyzing thousands of patterns of DNA cut by different enzymes; "jumping" along the chromosome to avoid unclonable regions; and finally, "walking" along the DNA by lining up overlapping segments of DNA into one continuous sequence. Several candidate genes then had to be further characterized to finally identify the gene presumed to cause CF.

After this CF gene locus was identified, the same part of the DNA was examined in CF patients. Many patients had the same defect: just three of the roughly 250,000 building blocks of DNA (nucleic acid bases) in the CF gene were missing. This little omission led in turn to the absence of just one corresponding amino acid in the chain of amino acids making up the CF protein product that is coded by the gene. The protein that is produced from the CF gene, called CF transmembrane conductance regulator (CFTR), is a type of membrane protein involved in moving ions, including chloride, in and out of cells. The CF deletion appears to occur in a location important to regulation of the molecule's activity. This is entirely consistent with the evidence that the fundamental CF defect is in regulation of chloride transport.

Continuing research on chloride transport will complement studies of the abnormal protein encoded by the CF gene. It is known that the CF defect lies in regulation of chloride channels rather than in the structure of the channels themselves. Regulation of these channels is proving more complex than expected. In normal individuals, chloride channels are regulated by at least two enzymes, called protein kinases, which chemically alter the channel (by phosphorylation). In cystic fibrosis, regulation of the channel by these enzymes is abnormal, apparently because the CF defect alters the target site on which the two enzymes normally act. NIDDK-supported investigators have also been able to isolate chloride transport channels from epithelium, take them apart and reassemble them in vitro. The way in which the defective CFTR protein compares with the normal can be investigated directly in such systems. In addition, "immortal" cell lines have been established that display characteristics of epithelial cells and chloride ion channels, and are useful for study of normal and defective CFTR.

CF provides an outstanding example of the crucial role that advances in basic science have played in the Institute's clinical research program. Underlying the discovery of the CF gene is research over the past forty years relating to the structure of DNA and its role in heredity; the ability of enzymes to cut DNA and to make copies of it; the genetics of bacteria and viruses, which are essential to cloning DNA; and the ability to understand protein structure, lipid structure, ion transport, and the regulation of cell processes. NIDDK has provided support to investigators in all these major areas of research, building a basis for understanding the workings of cells. Without this basis, CF would still be a mystery. Now, hope is high that our new knowledge of CF may lead directly to methods for bypassing the defective chloride ion channel regulation mechanism; and ultimately, to drugs that could alter the defective CFTR protein molecule, or to gene therapy to replace the erroneous gene and resultant abnormal protein with a normal molecule. In addition, this knowledge of the CF gene will make it feasible for individuals to determine whether they carry the CF gene, and thus are at risk of parenting a child with this fatal disease. Since one person in 20 carries the gene, this is an opportunity that will affect millions of Americans.

Diabetes

Today, there are more than 11 million diabetics in the United States, half of them undiagnosed. This number is more than twice the population of the Baltimore-Washington metropolitan area. Although diabetes affects individuals in a myriad of ways, all diabetics share the same need for effective therapies that will help to maintain, or improve, the quality of their lives. This need is being addressed through the research of biomedical scientists. It is through their efforts that an improved understanding of diabetes can lead to treatments to improve and extend human life.

Since its establishment 40 years ago, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has served as the government's lead research arm to provide exactly this hope for the nation's diabetics. True to their mandate, NIDDK scientists and grantees have vastly advanced the body of knowledge on diabetes during this period.

Today the quality of a diabetic patient's life is far better than when the Institute was established in 1950. At that time, people with diabetes were often sickly and highly dependent individuals. Although diet and insulin injections helped to keep diabetic patients alive, there were no effective treatments for the complications accompanying the disease. Furthermore, scientists knew very little about the biochemical basis of diabetes. An important initial step was the recognition that there are two major forms of diabetes, Type I, or insulin-dependent diabetes mellitus (IDDM), and Type II, or non-insulin dependent diabetes mellitus (NIDDM). In IDDM, an autoimmune process causes destruction of insulin-producing cells of the pancreas. In NIDDM, the disease results from an array of defects in the secretion and action of insulin, rather than from the initial destruction of insulin-producing cells. This form of diabetes has a particularly large impact on the health of several minority populations in the U.S., including Blacks, Hispanics, Native Americans, and Native Hawaiians.

For the individual diabetic patient and his or her family, perhaps the most important progress in NIDDK's 40 year history has been the increased independence and autonomy that research has provided. For example:

- Home blood-glucose monitoring kits have become a reality. On a practical level, this means that people with diabetes can live much more freely. They no longer have to visit the doctor's office solely for blood-glucose tests. Instead, these tests can be performed efficiently and inexpensively in the comfort of their homes. On a therapeutic level, this advance has been equally important. Formerly doctors were dependent upon urine tests which were slow in reflecting changes in the blood. Diabetics also can now perform blood-glucose tests more frequently, and thus can rapidly adjust their insulin regimens when blood-glucose tests indicate the need. This can lead to better control of blood glucose and to avoidance of life-threatening hypoglycemic episodes.

- Researchers have produced synthetic human insulin through genetic engineering techniques. Previously, cow and pig-derived insulin were the only sources of this therapy. Although these animal insulins were highly effective, they sometimes produced side effects, such as allergic reactions and loss of subcutaneous fat. Now, with genetically engineered human insulin, researchers have diminished the problem of immunologic side effects, because recombinant insulin is a human product. Moreover, they have made possible a uniform, lasting supply of this essential hormone, thereby ensuring that insulin therapy will always be available.

- Sophisticated blood tests have been developed to aid in assessing diabetic control. Researchers developed a test that measures the blood level of hemoglobin bound to glucose molecules, an undesirable product related to diabetes complications. By monitoring these glycosylated hemoglobin levels, doctors can better assess the effectiveness of diabetic control over time, thereby allowing them to restructure diabetic therapy if needed.

- Implantable insulin pumps are being developed that can also deliver insulin effectively. Recently, a pre-programmed implantable insulin pump was tested in 18 patients, and proved workable for over two years. While blood glucose must still be closely monitored, the pump delivers doses of insulin, offering patients the option of freedom from frequent insulin injections. It is hoped that this technology will be improved even further through the development of an implantable automatic "sensor" that can determine precisely when and how much insulin the body requires.

Today, physicians also can offer effective treatment for some diabetic complications. For example, biomedical research has clarified much of the mystery surrounding diabetic neuropathy -- a nerve-damaging disorder that strikes a large segment of the diabetic population, sometimes resulting in limb amputation. Investigators have determined that diabetics who suffer the tingling sensation associated with this complication develop destructive chemical abnormalities. One such problem is the formation of links between glucose molecules and proteins. To prevent these molecular errors, clinicians are testing the drug aminoguanidine. Another type of chemical problem that is involved in neuropathy concerns the abnormal metabolism of a class of molecules called polyols. Compounds called aldose reductase inhibitors seem to counter this defect, and are currently being tested for clinical value.

Progress also can be reported for diabetic kidney disease -- a disorder that produces kidney failure, and often death, in 30 percent of diabetics who have had the disease for more than 20 years. Scientists report that increased blood pressure in the kidney may be a cause of this condition. To combat it, researchers developed, and are testing, anti-hypertensive medications to control elevated renal blood pressure. In addition, a major clinical trial, the Modification of Diet in Renal Disease (MDRD) Study is under way to evaluate the effects of two dietary regimens on the progression of kidney disease. Type II diabetics are among the patients being studied in this trial.

The NIDDK is supporting a major clinical trial that may have a profound influence on the future treatment of diabetic patients. This study, the Diabetes Control and Complication Trial (DCCT), seeks to determine whether maintaining glucose levels close to normal can prevent, delay, or ameliorate the vascular complications of diabetes.

In another area of study, research funded by the NIDDK and the National Institute of Child Health and Development (NICHD) has contributed significantly to understanding and managing diabetes in pregnancy. Recently, for example, NIDDK grantees reported that pregnant women who suffer from gestational diabetes may be glucose intolerant before their pregnancy, and that the condition has gone previously undiagnosed. Thus, gestational diabetes may not originate in pregnancy.

Finally, laser therapy has proven extremely effective in patients with diabetic retinopathy -- a potentially sight-robbing complication that affects about 40 percent of all diabetics. Researchers know that retinopathy occurs when blood vessels in the retina swell, causing fluid to leak from them. Using special lasers, National Eye Institute (NEI) scientists were able to pRaub the blood vessels. In fact, studies show that in proliferative retinopathy, an associated disorder, vision loss can be reduced as much as 60 percent.

Since the Institute was founded, NIDDK scientists and grantees also have made enormous progress in understanding the molecular basis of diabetes. An excellent example of this progress is the current scientific pursuit of a marker, or genetic flag, in individuals at risk for developing IDDM. Such a highly specific marker was unthinkable given the state of technology 20 years ago. But technological advances in molecular biology have allowed scientists to scrutinise the body's biochemical signals much more closely than ever before. For example, we now know that if an individual has antibodies in his or her blood to a specific protein present on the insulin-producing beta cells in the pancreas, his chances of developing IDDM are significantly higher than for those who do not produce these same antibodies. Likewise, it is now known that a mutation leading to substitution of a single amino acid in an antigen protein greatly enhances the risk of a misguided attack by the immune system on the pancreatic beta cells, thereby triggering IDDM. Although a definitive genetic marker has not yet been found, these are exciting times for diabetes research. The basic knowledge and the scientific tools now exist to ask and pursue the more specific questions that may solve the mystery of IDDM.

The puzzle of NIDDM is even more complex. Determining all the biochemical switches that can trigger this disease and its highly destructive complications is a challenge. Errors in insulin receptors, glucose transporters and proinsulin processing are examples of the many problems that may lead to NIDDM. Research has also uncovered an intriguing protein, amylin, that accumulates in beta cells of diabetics, and may be related to the decline of these cells. In composite, previous NIDDK supported research on NIDDM has:

- o Discovered the precursor molecule -- proinsulin -- from which the glucose metabolism-regulating hormone, insulin, is generated.
- o Identified the membrane-bound cell receptor to which insulin binds to signal a cell to begin metabolizing glucose for energy.
- o Learned that the number of insulin receptors on cells declines when exposed to insulin, a phenomenon called "down regulation."
- o Discovered defective glucose transport systems in diabetics.

Although arcane to the public, these discoveries are comparable to the photographs that the spaceship Voyager 2 provided the world's astronomers last summer. Each NIDDK initiative brought into focus an unseen aspect of the topography of diabetes. From these and fundamental discoveries elsewhere, basic researchers the world over have devised more efficient strategies to attempt to treat, and ultimately cure and prevent this disease.

Liver Transplantation

The famous American philosopher William James once wrote, "Faith in the fact helped create the fact." This simple, but profound, idea of man's determination goes far in explaining many of our nation's finest scientific achievements. Since its establishment, NIDDK has witnessed this principle in the work of its scientists and grantees. However, one area of NIDDK-supported research to which these words are especially meaningful is liver transplantation. In the span of 20 years -- 1963 to 1983 -- this once controversial procedure has progressed from an experimental concept to a scientifically sound treatment that today offers many end-stage liver disease patients life, in place of certain death.

The need for this life-saving treatment is strongly suggested in national health statistics. End-stage liver disease -- particularly cirrhosis -- is currently the ninth leading cause of death in the U.S., taking the lives of an estimated 27,000 Americans each year. Moreover, although other therapies are being studied, none presently exist for treating end-stage liver disease.

In 1987, 1,182 liver transplants were performed at 45 transplant centers in the U.S., with recipients having a one-year survival rate of 65 percent, and a five-year survival rate of 55 percent. For some conditions, the one-year survival rates range from 70 to 90 percent. This contrasts sharply with the state-of-the-art in 1981, when only 26 donor livers were transplanted -- and only 40 percent of those recipients achieved even a one-year survival rate. Based on these figures, it is clear that liver transplantation has advanced into an excellent treatment strategy in the battle against end-stage liver disease.

But before attaining this high level of success, liver transplant researchers faced a formidable task in developing the necessary techniques. Liver transplantation was not the subject of serious research prior to the mid-1950s. However, careful animal studies enabled researchers to formulate the first surgical procedure for human liver transplantation. It was performed in 1963, when Dr. Thomas Starzl, an NIDDK-grantee at the University of Colorado, placed a donor organ into the body of a terminally ill hepatic cancer patient. In principle, such an operation is not complex. However, because many end-stage liver patients are in extremely poor health and have abnormal vascularization patterns as well, liver transplantation can be an arduous undertaking. Twenty-five years of additional research have greatly refined the original surgical procedure, making it safer and more efficient. Today, for instance, surgeons utilize the venous-venous bypass technique that was developed by NIDDK grantees and eliminates the pooling of blood in drainage areas during the operation. This, in turn, allows surgeons more time to perform the procedure. Moreover, the venous-venous technique greatly reduces the excessive blood loss and renal failure that sometimes seriously compromised the health of earlier liver transplant recipients.

Another research hurdle for liver transplantation was donor organ preservation. Many donor livers are obtained hundreds, or thousands, of miles from the operating room, and must remain functional for several hours before transplantation. Thus, proper storage of donor organs is essential to the success of the operation. When liver transplant research was first broached in the 1950s, organ preservation techniques simply did not exist. In fact, until the mid-1970s, storage methods were highly tedious and severely limited the acceptable timing of liver transplantation. In 1984, however, science took another key step, when an NIDDK grantee developed a preservation solution that suppresses cold-induced tissue swelling. This improvement effectively doubled the time a donor liver remains usable -- to an average of 12 hours. As a result, donor organs can be procured from cities once considered much too distant, making more organs available to more patients. In addition, surgeons now have the time necessary to microscopically inspect a donor liver before entering the operating room, assuring a better quality graft; and patients need not be prepared for surgery until the organ is deemed satisfactory.

Certainly the greatest post-operative need during the last 25 years of transplant research has been more effective immunosuppressive therapies for preventing organ rejection. This gap in knowledge was bridged through animal studies, which provided the first immunosuppressive strategies for liver transplantation in the late-1950s. These investigations suggested that the agent azathioprine and the steroid prednisone formed the most effective immunosuppressive regimen available, and when taken together, the two worked synergistically in suppressing the immune system. This therapy was later modified to include anti-lymphocytic drugs.

In the early-1980s, immunosuppressive therapy was greatly enhanced with the introduction of the drug cyclosporin. An important advance occurred when an NIDDK grantee determined that a treatment combining cyclosporin with steroids more safely and effectively modified the immune response than the existing immunosuppressive regimen. Largely as a result of cyclosporin's arrival, the success and frequency of liver transplantation began to grow. Indeed, a 1983 National Institutes of Health Consensus Development Conference on the subject concluded that liver transplantation should be considered a therapeutic modality for end-stage liver disease.

During the past year, researchers found in preliminary studies that the experimental drug FK-506 effectively suppresses the immune system, but causes fewer side effects than cyclosporin treatment. If future studies prove successful, FK-506 could markedly increase the rate of successful liver transplantation, as well as reduce the need for costly retransplantation.

On its 40th anniversary, the NIDDK is proud to have participated in the technological improvements in liver transplantation that are extending the lives of over one-thousand Americans each year. The Institute has supported Dr. Thomas Starzl, one of the world's premier liver transplant researchers, for over 25 years. In recognition of his outstanding scientific achievement, Dr. Starzl is the recipient of a special grant that provides long-term, stable support. Other notable research activities sponsored by the Institute include development of the University of Wisconsin preservation solution, support of a liver transplant database, and distribution of liver tissue for research purposes, in addition to a wide spectrum of investigator-initiated research.

While progress in liver transplant technology has permitted the procedure to become a viable option for many, the Institute remains committed to understanding the mechanisms that underlie liver disease. Additionally, successful therapies are being sought to obviate the need for liver transplantation. An encouraging example of clinical research directed toward this end was recently reported in a leading scientific journal. In an NIDDK-supported randomized, controlled clinical trial of patients with chronic hepatitis C (formerly known as non-A, non-B), approximately 50 percent of patients treated with recombinant alpha interferon showed a "complete response." Future studies will focus on higher doses of alpha interferon over longer periods of time to achieve a sustained response. This Institute will also continue to vigorously pursue other beneficial therapies for liver diseases to prevent liver failure and to avoid the necessity for transplantation.

Kidney Dialysis/Transplantation

When the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) was established in 1950, medicine lacked any proven treatments to control end-stage renal disease. In fact, much like the plight of patients with fully developed AIDS, individuals with end-stage renal disease faced rapid and uncompromising death.

With the advent of effective kidney dialysis and renal transplantation, however, most chronically ill kidney patients no longer are confronted with such a dire prognosis. Indeed, recent statistics indicate:

- o During 1983 to 1987, over 20,000 end-stage renal disease patients underwent kidney transplantation operations. The current three-year survival rate for patients who receive a cadaveric donor kidney is 83 percent. For those who receive kidneys from a living-related donor, the three-year survival rate is 92 percent.
- o Kidney dialysis treatments currently provide a three-year survival rate of 51 percent. The highest survival rates are in younger patients. For example, individuals who were less than 25 years old when their kidneys failed have an over 85 percent three-year survival rate.
- o Over 111,000 Americans received hemodialysis at Medicare-certified end-stage renal disease facilities from 1983 to 1987.

NIDDK grantees have contributed significantly to these developments during the past 40 years. In kidney dialysis research, for instance, several NIDDK-supported initiatives have produced substantial benefits for end-stage renal disease patients.

The earliest of these was an NIDDK grantee's discovery in 1960 that a "no-stick" Teflon shunt -- an artery-penetrating device that connects a vein to an artery -- prevents the development of blood clots that halted use of the procedure. This simple, but revolutionary, idea provided the basis for regular and safer kidney dialysis, because without the threat of clotting, a shunt could be left in place for multiple uses. Before this, uremic patients received dialysis infrequently, because minor surgery was required before each treatment to re-attach the necessary devices to veins and arteries.

More recently, several other NIDDK-supported initiatives have helped to make kidney dialysis safer and less burdensome for patients with irreversible kidney disease. For example, the Institute supported much of the basic research that led to compact hemodialyzers. The original "king-sized" artificial kidney drew approximately one-fourth of a patient's blood into the dialysis machine at once. As a result, many already-sickened dialysis patients required transfusions during therapy to maintain sufficient blood levels. By reducing the size of the machines, NIDDK-supported researchers sought to reduce the amount of blood required to fill them. To this end, basic researchers from various fields -- nephrology, hematology, bioengineering, and biochemistry -- collaborated during the past three decades to produce the smaller hemodialysis machines that now predominate the industry. Roughly the size of a fire extinguisher, these smaller models are dramatically reducing the need for blood transfusions in dialysis patients. Moreover, they are much more efficient -- decreasing the time required for each dialysis treatment from approximately six-to-eight hours, to about three-to-five hours.

Several other NIDDK-supported investigations have also increased the efficacy of dialysis treatment. For instance:

- Peritoneal dialysis has been refined to the point that it is now comparable in cost and efficiency to hemodialysis. In this alternative form of treatment, a patient's uremic waste is removed through flushing of the abdominal cavity with dialysate solution. This therapy is considerably easier to use and less risky than hemodialysis -- especially for home therapy.

- A portable artificial kidney has been developed for many dialysis patients. Interestingly, this highly compact device is completely independent of any plumbing connections. This research advance is possible because the unit's blood-purifying solution is constantly regenerated within the machine through sorbents that selectively bind undesirable waste products.

- A new concept of blood purification -- hemofiltration -- has been developed through biomedical research. It holds considerable promise for improved clinical results in the treatment of uremic patients.

- Many other aspects of dialysis patient care -- such as improvements in diet, prevention of chronic bone pain and fractures, and detoxification of uremic patients -- have been attained largely as a result of NIDDK-supported initiatives.

Kidney transplantation, meanwhile, has advanced from a procedure performed successfully only among twins or other family members to a state-of-the-art treatment with a very high success rate with cadaveric donors. With the present dearth of donor kidneys, less than half of the patients who are in end-stage renal disease now have the opportunity to undergo this life-saving operation. As more people recognize the opportunity to help others by donating organs, this rate is expected to increase markedly.

The NIDDK has supported research in renal replacement ever since the first successful human kidney transplantation operation involving a pair of Boston twins during the mid-1950s. In fact, the Institute has supported numerous research efforts in each of the four major areas of transplantation research: surgery, organ preservation, tissue typing and immunosuppression.

Because the kidney was the first organ to be successfully transplanted in humans, many of these early Institute-supported studies laid the groundwork for other organ transplantation operations, such as liver and heart transplantation. Notably, the first successful immunosuppressive regimen -- steroids and the chemotherapy drug azathioprise -- were tested in kidney transplant patients, showing for the first time that donor organ rejection was a highly reversible and controllable process. It is important, however, to underscore that researchers were in large measure able to perform experimental kidney transplantation research because renal dialysis was available. Unlike patients with other terminally diseased organs who have no other option than transplantation, a patient who failed to accept a replacement kidney could still be kept alive on a dialysis machine. The complementary relationship of the two treatments has gone far in sustaining and improving the lives of thousands of Americans.

Although both therapies are extremely successful, they are of course no substitute for the healthy kidneys with which most individuals are born. For this reason, NIDDK scientists and grantees continue to explore the basic mechanisms of renal function and disease with the aim of learning how to prevent end-stage renal disease. But, until the day that our understanding of renal dysfunction dictates that no one ever need lose a kidney to disease, most of the millions of Americans who today suffer from irreversible renal disease can rest assured that because of biomedical research, their disease does not mean certain and unyielding death.

Conclusion

As this retrospective clearly indicates, NIDDK-supported basic research is a 40-year story of continuous scientific progress. But there are many other chapters to the Institute's history that are now being written with respect to other diseases and disorders such as: inflammatory bowel disease, interstitial cystitis, osteoposrosis, sickle cell anemia, and obesity.

As the Institute enters its next 40 years, it is very proud of its accomplishments, but also mindful that research offers no guarantee of finding cures or miracle drugs. Nevertheless, biomedical research remains one of the nation's greatest hopes for the future. For, only through basic science, can our nation counter-attack and defeat diseases that rob Americans of their lives prematurely. To this special mandate, NIDDK scientists and grantees remain strongly and enthusiastically committed.

AIDS Research Program

Intramural Program

Despite significant advances in acquired immunodeficiency syndrome (AIDS) research, many fundamental questions remain unanswered about the disease and its treatment. NIDDK Intramural researchers remain committed to applying their basic research expertise to the high-priority fight against this public health menace.

The NIDDK intramural program is engaged in promising efforts to develop anti-viral agents to fight AIDS. Neurological complications strike nearly 60 percent of all AIDS patients, leaving many extremely disoriented for long periods of time. Therefore, a special need has arisen for drugs that can assail the human immunodeficiency virus (HIV) in the brain. NIDDK researchers are now evaluating three newly synthesized derivatives of the clinically effective HIV drug dideoxycytidine (DDC). Each DDC derivative is designed to penetrate and cross a tightly woven network of protective capillaries, called the blood-brain barrier (BBB). Once the drug passes the BBB, a series of biochemical reactions first lock the derivatives into the brain, then convert them into fully functional DDC. This research builds on the fact that DDC possesses a proven ability to fight HIV's reverse transcriptase activity -- the integration of its genetic material into the DNA of immune cells -- but is unable to cross the BBB. Recently, NIDDK scientists successfully developed techniques that accurately measure DDC derivatives in the blood and brain. These assays, which are now being carried out in animal studies, should indicate whether the compounds can cross the BBB while maintaining their anti-HIV properties.

In another study, NIDDK researchers are attempting to produce better derivatives of the drug azidothymidine (AZT). Currently, the standard form of AZT must be modified by infected cells, receiving a phosphate group that converts the drug to its active form. The researchers hope that their synthetic derivatives will be able to fight HIV infection directly, without modification by the cell.

The NIDDK has long been recognized for its technological expertise in determining the molecular basis of protein interactions. Extending this expertise to AIDS research, NIDDK investigators are now engaged in an effort to develop highly targeted agents to inhibit the reverse transcriptase and protease enzyme activities that allow HIV to insert its genetic material into the DNA of the body's immune cells. In this research, the scientists have adopted methods from various research disciplines, such as enzymology and analytical chemistry, in a rational approach to model drugs that interact effectively with HIV.

In another study, NIDDK scientists have begun to examine the three-dimensional structure of both HIV and human immune system proteins. Of the HIV proteins being examined, each plays an important role in either virus processing or replication. These studies, too, could one day yield more rational approaches to designing drugs against HIV.

For HIV to grow and reproduce, key proteins must interact with responsive genetic material elsewhere in the viral genome. This action is termed "in trans" because the protein exerts its effects elsewhere. NIDDK researchers, in a novel approach to thwart HIV growth and replication, are exploring whether a trans-acting protein produced by a gene from a benign human virus, adeno-associated virus (AAV), can interact with the HIV regulatory gene *tat*, and thereby inhibit the HIV gene's protein production.

In another study involving the *tat* gene, NIDDK investigators are developing new assays to test *tat* gene protein function. In laboratory tests, they have already learned that *tat* proteins markedly increase HIV transcription activity. If the function of these proteins can be better characterized, this knowledge could lead to new AIDS prevention and treatment applications.

HIV integration into the host cell DNA is a necessary step for the virus to efficiently replicate itself and spread to other cells. The integration step of the retroviral life-cycle is therefore a strong candidate as a target for anti-retroviral drugs. NIDDK scientists have developed a cell-free system that accomplishes retroviral DNA integration with cloned viral proteins. This system is being exploited to study the detailed molecular mechanism of integration. In addition, it is being developed as a simple assay system suitable for large-scale screening of potential drugs that inhibit integration.

NIDDK investigators also are examining the biochemical structure and function of the CD4 receptor -- the molecule to which HIV binds as its port-of-entry into the body's T cells. By so doing, the scientists hope to gain fundamental knowledge that will allow them to design strategies to block this process. To date, the researchers have developed several CD4 variants, many with pinpoint mutations, to allow them to understand the exact biochemical factors that must be present for HIV binding.

Extramural Research

The NIDDK supports AIDS research in all three of its categorical extramural divisions. Current projects are investigating HIV's effects on the endocrine, digestive, genitourinary, renal and blood cell systems, and the metabolic basis of the profound wasting and cachexia that often hastens the death of AIDS patients.

HIV-infected children sometimes suffer from gastrointestinal problems, such as chronic diarrhea. Many, in fact, have low body weights that may be due to their gastrointestinal problems. Recently, NIDDK grantees reported that microbiological analyses of fecal and intestinal samples from 14 children with AIDS showed that HIV directly causes these children's gastrointestinal disorders. This finding is significant because researchers previously had not implicated HIV as the source of this problem. Now that the anti-HIV drug AZT is available for children suffering from AIDS, perhaps these gastrointestinal problems can be overcome.

In another study of HIV-infected children, NIDDK-supported investigators determined after examining over 150 children with AIDS that those who acquire the disease in the womb sometimes develop renal complications, especially focal glomerulosclerosis -- scarring of the kidney's filtering glomerular cells. However, of the 150 children, the 12 children who suffered from kidney disease have not died from renal complications.

NIDDK grantees also recently investigated the nutritional status of over 50 adult AIDS patients. Because these patients consume fewer calories than healthy individuals, the research team found that nutrition may be a major predictor of an AIDS patient's survival. Moreover, these studies indicate that the rate of decrease in the complex protein albumin in the blood of these patients may define a function that limits their survival.

In another NIDDK-funded study, grantees found that HIV may directly infect megakaryocytes, large bone marrow cells that release mature blood platelets. Previous studies yielded no such evidence of direct HIV infection. Rather, the abnormalities seen in megakaryocytes were thought to be caused by other immune cells, such as lymphocytes and monocytes, which the AIDS virus had infected. This finding may help explain why some AIDS patients have a severely lowered level of blood platelets, a condition called thrombocytopenia.

National Institute of Diabetes and Digestive and Kidney Diseases

Diabetes, Endocrinology, and Metabolic Diseases

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$249,927,000	$260,093,000	+$10,166,000

Purpose and Method of Operation

The major program areas of the Division of Diabetes, Endocrinology and Metabolic Diseases foster basic, clinical, applied, and developmental research through the use of investigator-initiated research grants, program project grants, research center grant awards, research career development awards, Small Business Innovation Research awards, and research and development contracts. Training of individuals for research careers and/or teaching is accomplished through National Research Service Awards.

Diabetes

The fifth leading cause of death by disease in the United States is diabetes. The disease affects 11,000,000 individuals in this country, many of them children. Complications of diabetes strike virtually every organ system of the body, including the heart, kidneys, nerves, and eyes. Minority populations -- Black, Hispanic, and Native American -- are disproportionately affected by diabetes and by its enormous cost burden, estimated at over $20 billion dollars per year.

IDDM: Insulin-dependent diabetes mellitus (IDDM), also called Type I or juvenile diabetes, occurs when a patient's own immune system mistakenly attacks and destroys the insulin producing beta-cells of the pancreas. One of the major recent findings about IDDM is that, although the patient may become rather abruptly ill at the onset of the condition, the underlying process of beta-cell destruction has invariably progressed over a period of months or years prior to clinical disease. NIDDK grantees are searching for markers to identify individuals who will eventually develop diabetes, before they become clinically ill. These individuals may respond much more successfully to immunosuppressive or other treatments. Recently, researchers have discovered that a single amino-acid position within an immunomodulating protein can confer susceptibility or resistance to IDDM. Other NIDDK supported investigators have demonstrated that development of antibodies to a protein of the beta-cell, 64K antigen, is related to the appearance of IDDM. The use of such markers may allow intervention early enough in the disease to improve response to treatments that ultimately fail once the patient is clinically ill.

This recent understanding of the disease process has led to promising attempts to prevent diabetes by using immunosuppressive agents. NIDDK grantees have attempted such an intervention, utilizing the drugs azathioprine and prednisone, immediately upon diagnosis of the disease. As with earlier studies of cyclosporin, these patients improved; but the benefit decreased beyond one year of therapy. Studies such as this suggest that such interventions after clinical onset of IDDM are probably too late to succeed. The search for more specific and less toxic immunosuppressive treatments is continuing. Progress in this area will depend upon increased understanding of the basic disease process in man and in animal models of IDDM and other autoimmune conditions.

Institute-sponsored research is also examining the details of the immune response that destroys beta-cells in the first place. Specific lymphocytes that attack only beta-cells have been isolated from the pancreas. NIDDK-sponsored researchers have isolated and cloned cell lines of these lymphocytes from a mouse model of diabetes. These studies should enable much greater understanding of the details of the immune response and the destruction of beta-cells.

NIDDM: Most diabetic individuals in the United States suffer from noninsulin-dependent diabetes mellitus (NIDDM), commonly called Type II or adult-onset diabetes. These patients are unable to regulate blood glucose levels properly even though they may produce massive quantities of insulin. NIDDK-supported researchers have uncovered a wide variety of defects that may lead to this condition. Insulin normally acts on target cells by reacting with an insulin-specific receptor in the cell membrane. This receptor binding sets off a chain of events in the cell that leads specifically to increased transport of glucose from the blood into the cell. Special insulin-sensitive transporter proteins have been discovered that perform this job under the control of insulin in normal cells. The significance of alteration in just one base in the DNA coding for the insulin receptor has been described by an NIDDK investigator and his collaborators in work with patients who have severe insulin resistance. Patients with NIDDM can now be examined for genetic variations in the crucial regions of the insulin receptor and the insulin-responsive glucose transporter. Eventually, understanding of these variations will lead to tailoring of potential therapies to suit the specific defect in each patient.

For many NIDDM patients, insulin secretion also appears to occur abnormally. In normal individuals, it is secreted in pulses approximately 90-120 minutes apart, while in NIDDM patients, the pulse pattern is altered. In addition, some patients accumulate deposits of an abnormal protein, amylin, in beta cells. NIDDK-supported researchers have isolated the gene for amylin from a human cell line. The gene has characteristics suggesting that its expression is regulated, and that amylin, like insulin, may be a secreted "hormone" from the beta cell. Aberrant accumulation of amylin is under intense investigation to determine its potential role in the abnormality of beta cell function in NIDDM.

These exciting advances relating to the mechanism of disease in NIDDM may lead to new, more effective, and more rationally designed treatments for the many different subsets of this disease.

Diabetes Control and Complications Trial: Research findings have suggested that control of the level of sugar in the blood of diabetes patients as close as possible to the normal range may delay or prevent devastating complications. The Diabetes Control and Complications Trial (DCCT) is a multi-center clinical trial designed to test whether very careful control of blood glucose levels can prevent, slow, or reverse the vascular complications of insulin-dependent diabetes. The 29 medical centers across the country that are participating in the DCCT recently have completed recruitment of over 1,400 diabetic volunteers necessary to complete the study. Although final results of the study will not be available for several years, useful information has already been obtained from the trial relating to management of patient care and the feasibility of establishing close control of blood glucose levels. The study has also revealed the surprising fact that patients undergoing the experimental close control regimen tended to gain weight unless carefully monitored. Preliminary results also suggest that normalizing blood glucose levels can slow deterioration of residual insulin secretion in Type I diabetes.

Programmable Implantable Insulin Pump: Patients who require insulin therapy must currently take this medication by repeated daily injections or through an insulin pump -- a mechanical device with a plastic tube and needle planted beneath the skin. An alternative is a programmable implantable medication system, which is implanted in the abdominal wall and refilled with insulin every 2 months. It can be programmed in a variety of ways to provide the optimum insulin delivery for each individual and is controlled by the patient through a hand-held transmitter. The device has been implanted in 18 patients who have been followed for a total of 28 patient years. The experience thus far demonstrates the feasibility of this device for long term use in patients. Researchers are now working to develop a reliable implantable automatic glucose sensor that could monitor glucose levels constantly without intervention by the patient, thus rendering the pump fully automatic.

Treatment of Diabetic Complications: As researchers progress in understanding the various different processes that cause IDDM and NIDDM and in the development of preventive interventions, other investigators are developing treatments to help the individuals already suffering from these diseases. Many of the serious complications resulting in damage to kidneys, blood vessels, nerves and eyes occur in both types of diabetes. This damage results from at least two mechanisms: abnormal links between glucose molecules and proteins, and accumulation of sorbitol, a by-product of glucose metabolism. NIDDK grantees have contributed to research on development of drugs intended to prevent damage from both these processes.

Obesity: Onset and progression of NIDDM have been clearly and repeatedly linked to obesity. NIDDK-supported researchers studying the causes of obesity at the cellular level have arrived at some surprising observations concerning a fat cell product. Adipsin is a protein unique to the fat cell that is secreted into the circulation and whose regulation appears to be altered in several models of obesity. Rodent models of obesity have demonstrated up to a 100-fold reduction in levels of messenger RNA for adipsin. Adipsin is separate from the obesity genes in these animals, however, suggesting a regulatory role for the protein. In addition, mouse adipsin has been found to have the same activity as a human immune system component, complement factor D. The relationship between a fat cell product and the immune system is startling and provides a completely new perspective on metabolic control by the body.

Hyperproinsulinemia: Normally insulin is produced by the specific cleavage of a precursor molecule, proinsulin. When this process does not take place as it should, proinsulin levels rise in the blood. Since proinsulin has less biological activity than insulin, much more is required for the body function, placing a strain on the pancreas in order to maintain normal blood sugar in the patient. Previously, mutations had been identified that prevented the normal cutting of proinsulin to make insulin. NIDDK-sponsored researchers have recently discovered a different type of mutation that leads to the hyperproinsulinemia. In this case the mutation occurs in the insulin portion of the molecule and may be related to packaging of insulin into vesicles for secretion. Further investigation should yield insights into general mechanisms of secretion and protein processing.

Diabetes and Minority Populations: Minority populations suffer disproportionately from diabetes. At every age, Blacks are at greater risk of developing the disease than Whites, and suffer higher rates of complications such as amputation. Hispanics have a rate of diabetes twice that of Whites, with fully one third of the group 65-74 years of age suffering from the disease. In addition, Native Hawaiians appear to be particularly susceptible to the disease, and certain Native American populations display the highest known incidence of diabetes. In November, 1989, the Institute, in conjunction with the Indian Health Service, completed a series of workshops addressing diabetes in minorities. This meeting, Diabetes in American Indians and Alaskan Natives, was designed to focus attention of the research community on a unique research population and to facilitate communications with the Native American community in addressing the enormous impact of diabetes in this group. Understanding diabetes in minority populations not only has impact on the health of groups that bear a heavy burden from the disease, but also may help all patients by unraveling the genetic and environmental aspects contributing to the onset and progression of the disease.

Research Centers: Diabetes Endocrinology Research Centers (DERCs) and Diabetes Research and Training Centers (DRTCs) bring together basic and clinical investigators to create opportunities for new collaborations, training, and pilot and feasibility studies to further diabetes research. These centers also provide core resources, such as instrumentation, that can be shared among these investigators. In addition, DRTCs provide health professional training and model demonstration units for diabetes patient care and information. A recent example of research conducted at a center is a five year longitudinal study of depression in diabetic patients. Results of the study suggest that depression and diabetes may interact at a basic biologic level. This observation may lead physicians to devote greater attention to depression in the overall management of patients with diabetes.

Endocrinology

The various hormones, growth factors, and other hormone-like substances of the endocrine system affect nearly every process in the body. Thus, research on endocrine functions has relevance and application in virtually every disease and disorder -- for example, cancer, growth disorders, osteoporosis, and infertility disorders.

Growth Regulation: Since its isolation thirty years ago, growth hormone (GH) has been the mainstay of therapy for children with GH deficiency. In many cases, however, the GH deficiency is caused by an underlying problem in control of the pituitary gland by the hypothalamus. Preliminary studies conducted by NIDDK grantees indicate that the hypothalamic hormone that controls release of GH by the pituitary -- growth hormone releasing hormone (GHRH)--may have potential for the therapy of GH deficient children. This potential long-acting treatment might allow therapy for these children without the daily or three-times-weekly injections now required with GH. In addition, a small molecule has been discovered that selectively stimulates GH release from the pituitary by a different mechanism than GHRH. This hexapeptide may prove of therapeutic value alone or in combination with GHRH.

Classic hormones, such as growth hormone, may control growth by regulating local production of insulin-like growth factors (IGFs). These IGFs are synthesized by a variety of tissues and have potent growth promoting effects. Unlike insulin, however, IGFs are stabilized in the blood circulation by binding to specific proteins and may remain undegraded for many hours. NIDDK-supported researchers have uncovered a host of specific IGF-binding proteins that occur in a wide variety of sizes, differ from tissue to tissue, and are believed to play a key role in modulating tissue-specific effects of the growth factors. Human skin fibroblasts alone produce at least five different specific IGF binding proteins that are hormonally regulated. The importance of such proteins to growth is underscored by another line of NIDDK-supported research demonstrating that African Pygmies have normal levels of GH, but only half the levels of GH binding protein found in non-Pygmies. Unraveling the mechanism of regulation of IGFs and their binding proteins is an exciting avenue for investigation of disorders of human childhood growth and for understanding disorders such as diabetes and cancer, in which regulation of cell growth is disturbed.

Adrenal Hyperplasia: A variety of genetic defects of adrenal steroid production can lead to disease states. These range from a mild deficiency in the enzyme 21-hydroxylase causing increased facial and body hair and infertility in women to a rare, severe defect that leads to a potentially fatal syndrome of salt wasting in the newborn. Recent NIDDK-sponsored research has uncovered some of the mutations responsible for these disorders. Diagnostic tests based on this information will be especially important in the immediate treatment of salt wasting after birth. Continued research will focus on understanding how the errors in enzymes of the adrenal steroid synthesis path lead to disease.

Osteoporosis: Osteoporosis has been called the "silent" condition because it often progresses without any symptoms. It is a disease of major scientific and public health importance. Osteoporosis accounts for over 1.3 million fractures each year -- fully one-third of American women aged 65 or over will eventually have a spinal or vertebral fracture due to the gradual loss of bone. A variety of hormones are involved in normal bone metabolism, with bone disorders resulting when their complex interactions are disturbed. NIDDK-sponsored investigators have examined the roles of two of these hormones, vitamin D and parathyroid hormone, in osteoporosis. Decreased production of the active form of vitamin D is a characteristic of both osteoporosis and normal aging. In addition, a distinct abnormality in parathyroid hormone secretion has been identified in osteoporosis. Since parathyroid hormone has also been shown to regulate production of the active form of vitamin D, it seems likely that these interrelated hormones play a role in the development of osteoporosis. Research, which is continuing on the relationship between these hormones and the disease, may lead to new therapy for osteoporosis. Controlling the condition would help to alleviate an economic burden estimated at over $7 billion annually.

The therapeutic use of thyroid hormone has recently been shown to affect bone density. The hormone is administered to treat several conditions common in women over age forty. NIDDK grantees have demonstrated that an undesirable side-effect of even mild overtreatment with the hormone is reduction in bone density in some patients, possibly leading to osteoporosis. Fortunately, investigators have also developed a highly accurate blood test that permits detection of even subtle levels of excess thyroid hormone, so that dosage of hormone can be optimized to reduce the possible risk of osteoporosis. Investigators will continue to probe the risks and benefits of treatment with thyroid hormone.

Parathyroid Tumors: Few molecular genetic abnormalities have yet been described in benign tumors. Recent NIDDK-supported research has investigated the origins of adenomas (benign tumors) of the parathyroid glands. In a number of cases, the tumors appear to have arisen from a single cell that has undergone genetic alteration. In one case, the gene that codes for parathyroid hormone was rearranged with a region of chromosome 11 that is known to be the location of several oncogenes and of the gene for another disease affecting the parathyroid, multiple endocrine neoplasia. This gene rearrangement is a novel finding and raises the possibility that analogous rearrangements could be present in other benign tumors. Details of the chromosomal region involved are under investigation in an attempt to understand more fully how parathyroid tumors arise. In addition, an important assay has been developed by NIDDK researchers that allows accurate diagnosis of hyperparathyroidism and, when used during the course of an operation, provides information on whether removal of a single parathyroid gland is sufficient or more extensive exploratory neck surgery is required.

Metabolic Diseases

The human body is the site of hundreds of simultaneously occurring chemical reactions whose products interact and affect each other. When reactions occur in cells, tissues, and organs at the right rate and with the right concentrations of reactants, the outcome is the balanced normal state called homeostasis. If however, a genetic mutation alters one of the enzymes that helps maintain homeostasis, the upset balance results in disease. To discover how to correct such metabolic diseases, we need to understand the whole normal process by which information coded in the DNA is turned on and off, is translated into active protein molecules, and controls the activity of cells. Understanding these basic processes has applications in a wide range of metabolic diseases.

Cystic Fibrosis: NIDDK grantees this year have reported identification of the gene responsible for cystic fibrosis (CF). This prodigious effort required application of many of the tools of molecular biology developed over the past decade and has resulted in the immediate identification of the normal protein that is altered in CF patients. This protein, the cystic fibrosis transmembrane conductance regulator (CFTR), is a type of membrane protein normally involved in moving ions (salts) in and out of cells. Comparison of the DNA sequence of CF patients with that of normal individuals revealed that 70% of patients display the same error -- a three base deletion in their DNA -- resulting in a single amino acid missing from the CFTR. This deletion appears to occur in a location important to regulation of the molecule's activity.

NIDDK grantees also are studying the workings of cell membranes in normal and in CF cells. Chloride secretion through the epithelium in airway cells has been shown to be central in normal formation of respiratory tract fluid and clearance of mucus. In CF, concentrated mucus collects in the respiratory tract and leads to recurrent infection, ultimately causing patient death. Researchers have now been able to isolate chloride transport channels from epithelium, take them apart and reassemble them in vitro to investigate the transport process. In normal individuals, chloride channels are regulated by at least two protein kinases which chemically alter the channel. In cystic fibrosis, this regulation of the chloride channel is defective. While it is thought that CFTR is not the chloride channel itself, these membrane study systems should allow more direct investigation of its role in the disease process. Investigators have also been able to produce an "immortal" cell line that displays important cell characteristics, including chloride ion channels. This line can be used not only for study of ion transport, but also of cancer-like changes in airway cells.

Researchers will be striving to determine the role of CFTR, to identify membrane associated proteins and other components of transport systems which could be involved in the CF defect, and to elucidate control mechanisms for ion transport pathways. The new knowledge of CF may lead directly to methods for bypassing the defective chloride ion channel regulation mechanism, to drugs that could alter the defective CFTR protein molecule, to gene therapy to replace the erroneous protein with a normal molecule, and to diagnostic tests to detect carriers of the gene.

Application of Molecular Biology Techniques to Rare Diseases: Researchers supported by the NIDDK have applied new molecular biology techniques to a number of rare metabolic diseases. For example, a new method for amplifying DNA has been used to provide information about mutant DNA sequences present in families affected by Lesch Nyhan syndrome -- a terrible disease characterized by self-mutilation, spasticity and mental retardation. In one case, this analysis indicated that a patient's mother did not carry the mutant allele identified on her son's X-chromosome. This suggested that the mutation arose de novo and that future male offspring of this mother would have only a small risk of inheriting the disease.

In some cases, newly formed enzymes must be transported from their site of synthesis in the cell to another location, where they perform their function. NIDDK-supported researchers are unraveling the complicated molecular events involved in the production, modification and transport of the enzyme ornithine transcarbamylase (OTC) into the mitochondria. OTC deficiency resulting from an error in this process can lead to death from ammonia intoxication in newborn males. This research may also lead eventually to the ability to modify therapeutic agents so that they are transported to the specific cellular location where their action is needed -- a capability that would be of great value for a number of metabolic disorders.

Protein Engineering and Computer Modeling: Some enzymes, termed allosteric, can switch between active and inactive forms in response to changes in the local environment within the cell. This switch occurs through three dimensional structural changes that allow them to bind all the molecules needed to catalyze a biochemical reaction. Since such allosteric enzymes control whole metabolic pathways, they play a key role in regulation of cell metabolism. NIDDK-supported researchers have utilized the genetic engineering technique of site-directed mutagenesis to modify the enzyme OTC, which is not allosteric in normal cells, so that it displays characteristics like those of allosteric enzymes. This is the first time that protein engineering has succeeded in such a modification of enzyme properties. This line of research may be instrumental in controlling the expression of biologically significant proteins for therapeutic purposes.

Computer modeling studies utilize the data obtained from x-ray diffraction of crystallized proteins and convert this data into dynamic models that show how an enzyme's shape changes when various molecules bind to it. This technique has been applied to the enzyme glycogen phosphorylase, to elucidate how its shape changes when various molecules are bound. Glycogen phosphorylase is important in McArdle's syndrome, an inherited muscle weakness due to deficiency in the muscle form of the enzyme, and in Hers disease, a glycogen storage disorder caused by deficiencies in the liver form. The ability to visualize how protein structural changes affect enzyme activity will pave the way for researchers who design new biologically important proteins or engineer existing ones to modify disease states.

Rationale for the Budget Request:

The increase of $10,166,000 in FY 1991 over the FY 1990 estimate would enable these programs to support virtually the same numbers of awards as in FY 1990 in all mechanisms except research grants. The same number of research centers will be supported in FY 1991 as received funding in FY 1990. Other research grants and contracts will be funded at approximately the FY 1990 level. Research training would be maintained at the same number of trainees as in FY 1990.

An increase of 4.6 percent over FY 1990 average costs is proposed for noncompeting research project grants, and a 5.4 percent increase over FY 1990 levels is proposed for new and competing projects; however, approximately 2 more research project grants will be supported in FY 1991 than in FY 1990.

42

National Institute of Diabetes and Digestive and Kidney Diseases

Digestive Diseases and Nutrition

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$119,170,000	$123,916,000	+$4,746,000

Purpose and Method of Operation

The major programs of the Division of Digestive Diseases and Nutrition foster basic, clinical, applied, and developmental research through the use of investigator-initiated research grants, program project grants, center grant awards, research career development awards, and research and development contracts. Training of individuals for research careers and/or teaching is supported through National Research Service Awards.

Digestive Diseases

Digestive diseases and their long-term complications have catastrophic social and economic consequences. Approaching a cost to the nation of $50 billion annually in lost productivity, lost wages, and medical costs, they affect more than one-half the U.S. population at some time during their lives. The NIDDK supports basic and clinical biomedical research and research training on the normal function, pathophysiology, and diseases and disorders of the gastrointestinal tract and associated organs.

Gallstones: Although surgery remains the time-honored treatment for gallstones, alternative therapies have been introduced in recent years with the objective of dissolving the stones while leaving the gallbladder intact. Reports of European studies now confirm that one technique, extracorporeal shock-wave lithotripsy combined with bile acid therapy, is a safe and effective treatment in selected patients. With the aid of ultrasound imaging, this therapy generates shock waves that focus on the gallstones and fragment large stones into small ones. In the United States, several clinical trials testing variations of the lithotripter will enlist patients with intact gallbladders for future studies. The target of such studies will be to uncover predictive factors for gallstone recurrence in one-half of the treated population and preventive factors in the other half. A second nonsurgical approach instills an ether solvent directly into the gallbladder. This therapy has progressed, with NIDDK support, to development and patenting of a pump to control the volume and pressure of the infused fluids. This research advance promises to eliminate the potential for overflow and absorption of the solvent into the intestine.

Gallbladder disease is a recognized complication of obesity, and obesity is a risk factor for development of cholesterol gallstones. However, it also appears that rapid weight reduction itself can foster the formation of gallstones through reduction in bile acid secretion. Recent Institute-supported studies in obese patients on a rapid weight loss regimen revealed that caloric restriction predisposed these patients to develop gallstones. In contrast, patients who were administered a naturally occurring bile acid or aspirin did not show diet-induced gallstone formation. These research findings provide an important model to study more precisely how gallstones may be prevented and treated. Two other major discoveries are extending the reach of our knowledge concerning the maturation of gallstones from cholesterol crystals. The first is that cholesterol is secreted from the liver into bile as vesicles. Some alteration in the composition of these sac-like structures apparently enables formation of cholesterol crystals. The second discovery is the role that protein inhibitory and promoting factors have in favoring crystallization of cholesterol from bile. Understanding the basic mechanisms involved in gallstone formation is essential to devising physiologic or pharmacologic methods to prevent gallstones and to avoid recurrence of stones once they have been removed.

Liver Disease: The twenty years since the advent of human liver transplantation have witnessed major advances in immunosuppressive therapy and improved surgical techniques. Now a new organ preservation solution is being hailed as the third major advance in transplant technology and is revolutionizing the procedure at almost every level. In a recently reported study, a large series of liver transplants preserved with the new University of Wisconsin (UW) solution -- which helps prevent tissue swelling and cell deterioration -- was evaluated against grafts preserved with the conventional solution. The UW-preserved grafts survived at a higher rate, permitted equal numbers of patients to survive, had a lower rate of nonfunction and blood clotting, and had a reduced need for retransplantation. By effectively doubling the time that a donor liver can remain usable, the UW solution enables these organs to be transported and transplanted on a worldwide basis. Not only does this NIDDK-sponsored medical achievement provide a real therapeutic alternative to an otherwise emergency treatment, but it also promises to reduce the hospitalization cost of a liver transplant by lessening the chance of organ rejection. The development of this solution is expected to have widespread application to all forms of organ transplantation. In another Institute-supported effort, donor organs will be conserved through the use of a new liver function test, called the MEGX test, that demonstrates good predictive value in the selection of donor livers, allowing the use of some livers that would otherwise be rejected by less discriminating tests.

A most recent cardinal achievement in liver transplantation is a "stunning success" reported by NIDDK grantees with a new immunosuppressive agent, called by its code name, FK 506. Discovered in Japan in 1984, this agent was used by investigators with impressive results in the first clinical trials of an immunosuppressant that is unrelated chemically to cyclosporin and other standard immunosuppressants. Cyclosporin is the conventional therapy used in transplant surgery to suppress the immune system so that it is unable to reject the newly grafted organ that is recognized as an outside invader. However, cyclosporin's toxic effects and other limitations have stimulated a search for alternative agents. In these early trials, the efficacy of FK 506 was tested, both as a rescue protocol to salvage liver grafts from rejection, despite treatment with cyclosporin, and for primary immunosuppression in high-risk patients. It appears that the drug's mechanism of action inhibits production of certain immune system cells called lymphocytes, and its use was proven to be "remarkably free of unwanted effects." This exciting discovery offers the prospect of a new era in transplant surgery that will allow several organs to be transplanted at the same time for the treatment of cancer and many other diseases, including juvenile diabetes. It also presents opportunities for treatment of other ailments caused by auto-immune diseases, such as Crohn's disease and ulcerative colitis. In addition, by reducing the number of rejected organs, FK-506 may permit people awaiting an initial organ transplant to receive many of the organs presently used for re-transplants. Not the least of its significant benefits is a drastic reduction of costs, owing to hospital stays shortened by half from the in-hospital time required for those treated with cyclosporin.

The single most frequent indication for liver transplantation is primary biliary cirrhosis (PBC), a chronic liver disease. In a recent development, NIDDK grantees demonstrated that autoantibodies from the serum of patients with PBC react with at least three antigens of the mitochondria (cell components responsible for generating energy). Two of these antigens have recently been cloned and sequenced and their protein products identified. With the use of recombinant techniques, these advances have permitted rapid production of large quantities of highly purified antigen and the development of sensitive diagnostic assays for the detection of primary biliary cirrhosis. These findings will aid further investigations of antigenic exposure and genetic susceptibility and help to more readily uncover the mechanism that induces the appearance of these antibodies and the disease.

As part of its commitment to research into the normal and disease processes of the liver, the NIDDK supports a liver procurement and distribution system to provide researchers with discarded human tissue specimens from liver transplants. Another research resource -- a cell culture facility -- will develop means of maintaining human liver cells in long-term culture to be made available for the study of cell biology and cell function. NIDDK also supports a liver transplantation data base that is currently entering an operational phase. One-year survival rates in transplantation for some liver diseases, such as primary biliary cirrhosis, presently range from 70 - 90 percent. The data base will now focus on identifying ways to improve quality of life following the operation by minimizing or preventing the occurrence of complications. The data base will also aid the design of future clinical studies by providing access to an adequate patient population through its participating centers. For example, a clinical study might examine factors that account for poorer survival rates among patients transplanted for cancer, hepatitis, and fulminant hepatic failure. Important research questions can then be addressed on the relative therapeutic benefits of remedial therapies for these transplant recipients.

Inflammatory Bowel Disease: The causes of Crohn's disease and ulcerative colitis, collectively termed inflammatory bowel disease (IBD), are unknown, but it is believed that the immune system plays a major role. Among the cell types and mechanisms involved in cell-mediated immunity are special immune cells which produce mediators -- called lymphokines -- that activate killer-cell function. To determine whether a limitation on the quantity of these mediators may impair the immune system, Institute-sponsored scientists examined the contribution of killer-cell activity to local tissue damage. Using immune cells from the intestines of Crohn's and ulcerative colitis patients, they found less lymphokine activity in IBD cells when compared to control cells. However, after adding recombinantly-derived lymphokines, they found that cell-mediated activity was normal or increased in Crohn's cells, but definitely reduced in ulcerative colitis cells. The investigators concluded that reactivity of the responder cells to lymphokines distinguishes the normal immune response from the response seen in ulcerative colitis and Crohn's disease. Furthermore, factors other than decreased lymphokine production appear responsible for the abnormal killer-cell activity seen in ulcerative colitis. This advance is significant because defective killer-cell activity may contribute to the predisposition to cancer of some patients with ulcerative colitis, while normal activity can lead to the reduction or elimination of tumor growth. Reduced killer-cell activity in ulcerative colitis is an important area for future investigation and may be crucial to defining the local abnormalities involved in inflammatory bowel disease.

Ulcers: A bacterial organism, called Campylobacter pylori, is now known to be the most common environmental cause of acute and chronic gastritis. NIDDK grantees also postulate that it is an important factor in the origin and development of peptic ulcer disease. Gastric mappings undertaken by these investigators have demonstrated that the bacterium causes a progressive inflammation from the cavity to the body of the stomach, subsequent destruction of the stomach's acid secreting areas, and, ultimately, a pattern of gastritis. Additional studies evaluated methods for detecting the bacterium, including direct staining of endoscopically obtained organisms, a urea breath test, and an immunoassay for the presence of antibodies. Most importantly, these investigators demonstrated that they can eventually heal an ulcer and prevent its recurrence by eradicating the bacterial organism with combined bismuth and antibiotic therapy. These findings may ultimately lead to wide scale control of peptic ulcer disease, a condition that affects 10 percent of the American population.

Therapeutic Endoscopy: The past decade has witnessed an extraordinary transition in the use of the endoscope from solely a diagnostic tool to a therapeutic modality. To illustrate, one of the most dreaded complications of peptic ulcers is bleeding, an event that results in a mortality rate of six to ten percent despite advances in diagnosis and treatment. With the endoscope, light is channelled by bundles of glass fibers into the hollow organs of the body, providing direct access to the site of a bleeding peptic ulcer. Then, to effectively stop the bleeding, a heater probe is passed through the endoscope and placed against the bleeding ulcer, or an electrical current is delivered through the probe to the bleeding blood vessel. Of several approaches evaluated, these two techniques were determined the most promising modalities for endoscopic therapy by an NIH consensus conference recently convened by the NIDDK and the Office of Medical Applications of Research. The panelists agreed that the diagnostic accuracy of endoscopy identifies patients at high risk of persistent bleeding and rebleeding, allows for immediate treatment, and makes the need for surgery a rare event. Since the costs of surgery are typically twice that of endoscopy, this is an obvious benefit.

In another development, NIDDK grantees have succeeded in incorporating an ultrasound probe into the tip of a fiber optic endoscope. The ultrasound device allows physicians to see beneath the mucosal lining to determine whether or how deeply a tumor has extended into the organ wall of the stomach or esophagus. In fact, in recent studies this ultrasound image detected the presence of colon cancer in 88 percent of cases and determined the depth of invasion in 93 percent. In addition to effectively determining the stage of various GI tumors, the echo probe may be able to differentiate a benign from a malignant lesion, as well as to accurately judge the size and depth of ulcers and the thickness of the mucosa in inflammatory bowel disease. Investigators are also attempting to adapt the echo probe to provide real-time images of GI motility in a much more powerful way than current assessment techniques utilizing static pressure or balloons. This adaptation may provide new means for investigating the mechanisms underlying diseases such as diabetes and irritable bowel syndrome.

Digestive Diseases Research Centers: The NIDDK Digestive Diseases Research Centers provide the necessary catalyst to assemble established investigators who conduct high-quality research related to a common theme in digestive disease research. This goal is achieved through funding of core resources, pilot and feasibility projects, small conferences, and consultant services to the center. In a recent example of such collaborative research, investigators transferred normal genes into liver cells with defective genes by use of retroviruses that had previously taken up the normal genes. Introduced into liver cells in this fashion, the genes were shown to express their functional protein products. This advance represents an important preliminary step toward the long-term goal of achieving successful liver-directed gene therapy to correct various inherited metabolic disorders.

Nutrition: NIDDK fosters and supports research in the broad areas of fundamental and clinical nutrition. Studies focus on the action and interaction of nutrients within the body, environmental effects on problems of nutrient imbalance, and nutrient requirements in health and disease. In tandem with these activities, the NIDDK acts as the NIH focal point for the U.S.-Japan Malnutrition Panel, which was established in 1966 to define areas of interest that may result in investigator-initiated research directed at alleviating the serious problem of malnutrition in Asia.

Clinical Nutrition Research Units: An integrated array of research, educational, and related activities is fostered through NIDDK-supported Clinical Nutrition Research Units (CNRUs). Each of the CNRUs is located in a medical school environment and each is associated with an NIH-supported training program in nutrition. This structure not only attracts promising scientists to the field but helps to establish nutrition as a discrete discipline in these institutions. To support clinical nutrition research, core laboratories are also available to students, trainees, and investigators in such areas as metabolism, food intake, and vitamins and minerals. Added to start-up funding for pilot studies of new investigators and broad educational programs for medical students, these activities provide a focus for nutrition research that would not exist otherwise.

Obesity: Institute-supported research is attempting to unravel the multiple and complex factors that cause obesity. Some 26 per cent of U.S. adults 20 to 74 years of age, or an estimated 34 million Americans, are considered obese -- a statistical fact that glaringly illustrates the magnitude and seriousness of this growing public health problem. These Americans are at greater risk of developing diabetes mellitus, cardiovascular disease, hypertension, gallbladder disease, and certain forms of cancer. One confounding area of investigation deals with how the body adjusts its metabolism during and after weight loss such that calories are burned at a decreased rate. This phenomenon results in a metabolism that hinders weight loss, even when the intake of calories is restricted. To decipher this puzzling fact, NIDDK-supported researchers examined the effects of lean or muscular body mass, total body weight, and percent body fat on energy expenditure by comparing subjects who were matched in one of these body composition measures, but who differed in the others. Their results have shown that resting metabolic rate is a function of lean body mass, and not obesity *per se*. Thus, an obese person will burn fewer calories under resting metabolic conditions than a person of the same weight who is lean. In addition, the metabolic rate of non-obese persons normally increases in response to eating, cold exposure, or the combination of a meal plus exercise. However, this normal increase in metabolic rate under these conditions is diminished in persons who carry extra fat relative to their lean body mass.

Additional studies have been conducted to clarify the independent relationships of obesity and overweight to cardiovascular disease risk factors and sex steroid levels. A model was used similar to that designed for the earlier studies to uncouple the imputed relationship between these factors. Researchers found that total body weight is not independently related to either sex hormone levels or cardiovascular disease risk factors, whereas the individual body composition parameters, fat mass and lean mass, are significant determinants of both. Thus, body composition and not body weight is associated with increased cardiovascular disease risk, and alterations in sex steroids are related to body composition and are not an independent risk factor. These findings emphasize the importance of body composition rather than body weight or relative weight in determining energy expenditure and cardiovascular risk status. They will also provide an effective study design for future experiments on metabolic and clinical differences observed in overweight subjects as they relate to the lean body mass, fat body mass, percent body fat, or total body weight.

Total Parenteral Nutrition (TPN): Advances in intravenous feeding are carving major inroads into the nutritional management of very low birth weight infants. Because these infants are premature, they have poor intestinal function, are malnourished for several weeks after birth, and have immature respiratory systems. Until recently, very little information has been available regarding vitamin requirements during intravenous feeding of children. To remedy this deficit, NIDDK grantees have made a substantial commitment to developing and validating micromethods for analysis of specific levels of vitamins and nutrients. Their success has provided the only substantive data from which guidelines can be derived for vitamin use and has led directly to improved patient care and insights into other health implications for this at-risk population. For instance, almost one-half of very low birth weight infants have vitamin A deficiency, which scientists attribute to an 85 percent loss of the vitamin supplement that occurs in standard intravenous delivery. Researchers have now succeeded in preventing these losses by adding vitamin A to an intravenous lipid emulsion. Consequently, the incidence of a chronic lung condition linked to deficiency of vitamin A has been reduced. In other research using animal models, investigators have studied intestinal transport and defined for the first time the mechanisms and regulatory factors responsible for age-related changes in transport. At the same time, studies of components of intestinal cell membranes have provided a better understanding of how disease conditions and immaturity can affect nutrient absorption. All these findings dramatize the urgent need for modifying existing multiple vitamin preparations for use in premature infants and illustrate the need for continued evaluation of nutrients as other markers of nutritional status. In the future, research will focus on improved nutrient delivery to improve survival rates and reduce morbidity and hospital costs related to the care of premature infants in this subpopulation.

Rationale for the Budget Request:

The increase of $4,746,000 in FY 1991 over the FY 1990 estimate would enable these programs to support virtually the same numbers of awards as in FY 1990 in all mechanisms except research grants. The same number of research centers will be supported in FY 1991 as received funding in FY 1990. Other research grants and contracts will be funded at approximately the FY 1990 level. Research training would be maintained at the same number of trainees as in FY 1990.

An increase of 4.6 percent over FY 1990 average costs is proposed for noncompeting research project grants, and a 5.4 percent increase over FY 1990 levels is proposed for new and competing projects.

National Institute of Diabetes and Digestive and Kidney Diseases

Division of Kidney, Urologic, and Hematologic Diseases

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$122,470,000	$127,347,000	+$4,877,000

Purpose and Method of Operation

The major programs of the Division of Kidney, Urologic, and Hematologic Diseases (DKUHD) foster basic, clinical, applied, and developmental research through the use of investigator-initiated research grants, program project grants, research center grant awards, research career development awards, Small Business Innovation Research awards, and research and development contracts. National Research Service Awards support the training of individuals for full-time careers in research and/or teaching.

Kidney Disease

Kidney diseases and disorders are among the nation's most critical public health problems. In 1985, thirteen million Americans suffered from kidney and urologic diseases, at an annual estimated cost of $40 billion. The Federal Government now spends over $3 billion each year on treating end-stage renal disease alone. This includes direct costs for maintenance dialysis and kidney transplantations in a growing population exceeding 140,000 patients. High priority areas of research to combat kidney disease include: studies of the effects of hormones and diuretics on metabolism of the kidney; the effects of drugs and toxins; the immune system's role in the development of immune renal injury; mechanisms leading to chronic renal disease, including kidney disease of diabetes mellitus and polycystic kidney disease; renal transplantation and dialytic therapy; and therapeutic interventions for end-stage renal disease.

Kidney Disease of Diabetes Mellitus: A major research initiative of the Institute is in kidney disease of diabetes mellitus (KDDM), which is the leading cause of end-stage renal disease (ESRD) in the United States. Diabetic patients account for an increasing share of the total ESRD population. The number of patients with end-stage renal disease due to KDDM has risen steadily over the last decade to nearly 30 percent of new patients entering the ESRD Medicare Program. In addition, the 5-year survival of patients with KDDM who are receiving dialysis is less than one-half that of dialysis patients without diabetes mellitus. To provide an organized framework for research in this critical area, the DKUHD sponsored the second International Symposium on the Kidney Disease of Diabetes Mellitus in March

1989. This symposium brought together scientists from both the diabetes and nephrology research communities to review research needs in the areas of basic research, clinical studies, and epidemiology; and to foster interdisciplinary research between these groups.

A key problem identified by participants in the conference was the need for reliable measurements of kidney function for clinical assessment of patients. Without such methods, long-term studies of treatment alternatives and epidemiologic factors cannot be carried out effectively. A new method for assessing kidney function has been developed by NIDDK-sponsored investigators. The method, measuring renal clearance of three radioisotope markers, is now being used to assess renal function in several clinical trials, and in the study of kidney disease in the Pima Indians. NIDDK is encouraging research on: genetic factors, cell biology, and biochemistry of KDDM; model systems for the disease; and a variety of clinical and epidemiology studies.

Modification of Diet in Renal Disease: The Modification of Diet in Renal Disease study is a multicenter clinical trial designed to determine whether reduction of dietary protein and phosphorus, as well as strict control of blood pressure, can significantly slow down the progressive loss of renal function in persons with chronic kidney disease. The full-scale, randomized, controlled investigation is now under way at fifteen participating clinical centers throughout the United States. Approximately 800 patients will be randomized to one of two levels of blood pressure treatment targets and one of two protein and phosphorus-restricted diets. A Data and a Nutrition Coordinating Center and seven central laboratories provide support for this study.

Polycystic Kidney Disease: Polycystic kidney disease (PKD) is a hereditary and potentially fatal disease. This disease causes formation in the kidney of fluid-filled sacs known as cysts, leading to reduction and eventual failure of kidney function. PKD is a major cause of new patients entering into the ESRD Medicare Program. Some cystic kidneys and some renal cystic diseases clearly are hereditary in both humans and animals, with predictable patterns of inheritance.

While the origin and disease process of PKD remains unknown, NIDDK scientists are continuing to test hypotheses that have been suggested based on experiments with laboratory animal models. In these studies, it has been shown that several chemicals can cause progressive but reversible cystic changes in the kidney, similar to those seen in PKD. Changes in the basement membrane of the kidney were detected along with cystic changes, suggesting that the basement membrane plays a key role in cystic disease. These results also suggest that environmental factors may be involved in the development of PKD in humans. Research is continuing to characterize more precisely the underlying processes leading to cystic disease.

U.S. Renal Data System: In 1988, the NIDDK established the United States Renal Data System (USRDS) as part of an interagency agreement with the Health Care Financing Administration. The goals of this newly established data system are to: create a consolidated renal disease data system to describe and analyze trends; report regularly on incidence, prevalence, and mortality; identify the modalities of treatment best suited to various types of patients, through relevant research; and undertake more focused investigations, "special studies" of issues currently unaddressed. During its pilot phase, early analyses from existing data were conducted and recommendations were made to NIDDK on priorities for further special studies. The first USRDS Annual Report was published in August 1989.

Cyclosporin Nephrotoxicity: Toxic effects on the kidney are the most frequent and clinically important complications resulting from the use of cyclosporin, an immunosuppressive drug. NIDDK-supported researchers have developed new animal models for this clinical problem, providing evidence that abnormalities in fluid volume outside the cell contribute significantly to the decreases in renal filtration rate and blood flow that are associated with cyclosporin treatment. Early results suggest that it may be possible to reverse these drug-induced problems, lessening the severity of the toxic effects of cyclosporin. NIDDK grantees will continue to characterize the development of abnormal fluid volume in cyclosporin-treated animals, and to explore possible applications of their results to clinical medicine.

Urologic Diseases

The NIDDK supports research ranging from fundamental studies, such as understanding the materials that form kidney stones, to clinical projects, such as the comparison of medical versus surgical therapy for bladder abnormalities in children. Among the high-incidence urologic diseases emphasized in this program are urinary tract infections, reflux nephropathy, urolithiasis, benign prostatic hyperplasia, interstitial cystitis, erectile impotence, and urinary incontinence. Research efforts are focused on developing insights into the normal and abnormal functions of the organs and tissues of the genitourinary tract.

Interstitial Cystitis: Interstitial cystitis (IC) is a disorder of the urinary bladder that is diagnosed by most clinicians on the basis of subjective symptoms of chronic, debilitating pain and frequent urination not associated with other known causes. Until recently, a lack of objective criteria for assessment of the disease has impeded the design and interpretation of clinical studies and has also contributed to the lack of investigators in the field. An NIDDK-sponsored workshop was responsible for developing a uniform set of objective and subjective criteria for the diagnosis of IC. Use of these criteria now will be required in all NIDDK-funded research projects on interstitial cystitis. The first studies based on the criteria have demonstrated a deficiency in the protective layer of the bladder lining of IC patients that allows certain small molecules to pass through the lining. Studies may now be conducted to determine what causes the loss of the protective effects of the bladder lining in these patients and whether it is analogous to chronic inflammation of the prostate, which causes similar symptoms in men.

Recently, NIDDK initiated three new grants on interstitial cystitis. Two of the grants are for clinical research studies on IC and one is for the establishment of a pilot data base at an existing George O'Brien urologic disease research center. One of the clinical research grantees is studying the urine of IC patients for clues to the disease, and the other is examining the role of mast cells in the pathogenesis of IC. The pilot database is establishing a system for the acquisition of data on patients who have been diagnosed with interstitial cystitis. Both this system and the data may then be used in future studies.

NIDDK is continuing to work closely with the Interstitial Cystitis Association to combat this debilitating disease. The Institute hopes to pursue research leads that may emerge from a future workshop scheduled for the Spring of 1990, at which preliminary data from interstitial cystitis research projects will be presented.

Benign Prostatic Hyperplasia: Benign Prostatic Hyperplasia (BPH) is a localized noncancerous enlargement that occurs within different areas of the prostate gland and may result in significant difficulty in urination. The changes of BPH begin in young adulthood and are evident in the majority of middle-aged and older men. The harmful side effects of this disorder increase in incidence as men age. At this time, the only proven method for correcting advanced BPH is surgical excision of enlarged areas. NIDDK-supported research has examined the role of basic fibroblast growth factor in BPH. The factor is found in low levels in normal prostate tissues, but is present in higher concentrations in the regions of the gland where BPH occurs. This finding provides a possible new approach to retarding the development of BPH in its early stages without manipulating the male sex hormones (androgens). Androgens have been demonstrated to have numerous side affects when administered to the adult male. These side affects include erectile impotence, decreased libido, feminization, and enhancement of growth of undetected prostate cancer. Research is continuing on the causes of BPH and the development of new therapeutic agents to block this undesirable growth.

Impotence: The prevalence of impotence in diabetic men has been reported to be as high as 50 percent. The adverse effects of diabetes on the nervous system and blood vessels have been presumed to be responsible for this erectile dysfunction. For this reason, erectile dysfunction may serve as a model for providing further insight into the underlying disease process of diabetes as it affects blood vessels, smooth muscle, nerves and other organs.

NIDDK-supported researchers have reported a very significant finding on disorders of penile erection from investigations both in rats with chemically induced diabetes mellitus and in diabetic human males. They have shown that the smooth muscle of the male genital tract from the rats with chemically induced diabetes loses the ability to relax as readily as that of normal tissue after stimulation by chemicals released from the adjacent nerve. This finding is significant because the smooth muscle of the penis must relax for erection to occur. Relaxation of the muscle allows the perfusion of blood which engorges the sinuses in the penile tissue and distends and relaxes the smooth muscle. NIDDK-grantees will continue to study the effect of diabetes mellitus on the penile tissues and the other tissues of the urogenital system.

Hematologic Diseases

The NIDDK supports investigation into the basic mechanisms of normal blood cell function and of hematologic disorders. Insight into diseases affecting the formation of blood or blood cells may also provide an understanding of the basic processes of cell proliferation and differentiation.

Erythropoietin: When the kidney stops functioning, it no longer produces erythropoietin, a hormone that stimulates red blood cell production. As a result, ESRD patients are highly anemic, require repeated blood transfusions, display reduced ability to function, and experience diminished quality of life. A profound advance for the thousands of patients with ESRD has been the development of genetically-engineered erythropoietin, based on underlying NIDDK-supported basic research. This substance is a naturally occurring growth factor, produced primarily by the kidney, that stimulates production of red blood cells. The Food and Drug Administration has just approved human recombinant erythropoietin for use in end-stage renal disease patients. Now, thousands of patients with kidney failure are enjoying increased energy, improved appetite, and reduced need for transfusion. Erythropoietin may also prove valuable for patients with kidney disease that has not yet progressed so far as to require dialysis or transplantation. In addition, the recombinant hormone holds promise for other situations where growth of red blood cells is important. Recent NIDDK-supported research has shown the feasibility of using erythropoietin to increase the amount of patients' own blood that can be collected beforehand for use in a scheduled surgical procedure. Thus, this advance also has implications for AIDS.

Granulocyte-Colony Stimulating Factor: Bone marrow stem cells are the precursors for circulating cells of the blood. They develop into the various different types of blood cells under the influence of specific growth factors, which may also influence the function of mature, differentiated blood cells. NIDDK-supported researchers have studied a growth factor that stimulates development of undifferentiated stem cells into neutrophils, blood cells that can kill and digest invading microorganisms. This growth factor, known as granulocyte-colony stimulating factor, has been cloned and reproduced for human therapeutic use. The factor helps counteract a reduction in neutrophils in the blood of patients undergoing chemotherapy for cancer, thus helping to reduce the frequency and severity of infection and to improve survival rates for these patients. This growth factor may have an additional benefit of forcing malignant tumor cells to mature into differentiated forms that can no longer reproduce. NIDDK-grantees are currently conducting clinical trials utilizing this granulocyte-colony stimulating factor in conjunction with cancer chemotherapy. Future uses may include prevention or correction of neutrophil depletion induced by the drug AZT in the treatment of AIDS, and treatment of aplastic anemia.

George O'Brien Kidney and Urologic Research Centers: The aim of the George O'Brien Research Centers, initiated in 1987, is to develop the knowledge necessary for providing rational means to detect, prevent, and/or treat kidney and urologic diseases. Each center has a specific interdisciplinary research emphasis. These areas include immunologically mediated kidney diseases; diabetes mellitus and other endocrine and metabolic disorders; developmental and obstructive disorders of the kidney and urinary tract; primary renal hypertension; nephrotoxins and renal failure resulting from cell injury; and benign prostatic hyperplasia.

These centers are generating new knowledge that should aid in understanding and treating kidney and urologic diseases. For example, a research group at one George O'Brien center has demonstrated the presence of specific growth factors in the testes and semen. These factors stimulated cells of the prostate to grow at three to four times the normal rate. It is postulated that these factors may play a role in development of benign prostatic hyperplasia.

Rationale for the Budget Request:

The increase of $4,877,000 in FY 1991 over the FY 1990 estimate would enable these programs to support virtually the same numbers of awards as in FY 1990 in all mechanisms except research grants. The same number of research centers will be supported in FY 1991 as received funding in FY 1990. Other research grants and contracts will be funded at approximately the FY 1990 level. Research training would be maintained at the same number of trainees as in FY 1990.

An increase of 4.6 percent over FY 1990 average costs is proposed for noncompeting research project grants, and a 5.4 percent increase over FY 1990 levels is proposed for new and competing projects.

National Institute of Diabetes and Digestive and Kidney Diseases

Intramural Research Program

Authorization: Indefinite.

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
428	$68,728,000	439	$73,295,000	+11	+$4,567,000

Purpose and Method of Operation

For 40 years, NIDDK intramural research has helped to advance scientific understanding of human disease and medicine. Currently, over 200 research projects are being conducted in laboratory, clinical, epidemiological and biometric investigations in the Institute's Bethesda, Maryland and Phoenix, Arizona laboratories. NIDDK scientists, moreover, continue to collaborate closely with other NIH institutes, government agencies, and basic research laboratories throught the nation and the world, including leading groups in industry.

Diabetes

Non Insulin-Dependent Diabetes

Although noninsulin-dependent, or Type II, diabetes remains one of the most complex and multifaceted diseases known to man, NIDDK researchers are continuing to make progress in understanding the disorder. At the NIDDK's Phoenix Field Station, for example, researchers have monitored a group of high-risk, adult Pima Indians for many years. As part of this effort, they are now attempting to chronicle the metabolic changes that accompany this form of diabetes. The researchers hope that by knowing more precisely how the disease develops, they will be able to adopt strategies that interrupt its destructive advance. Their work has revealed that the first signs of Type II diabetes are weight gain and insulin resistance -- a finding that is important for early identification and treatment of Type II diabetes. Moreover, they report that, as cells initially grow resistant to insulin (the vital hormone that stimulates glucose metabolism), the body compensates by secreting more insulin into the bloodstream. In time, however, the body's ability to produce this essential hormone also deteriorates, leaving Type II diabetics unable to properly secrete insulin or metabolize glucose.

Diabetics frequently suffer from hypertension. It has been proposed that insulin resistance is responsible for this problem, as well as for the high levels of blood glucose and blood insulin that occur during the development of non-insulin dependent diabetes. Moreover, it has been suggested that all these features constitute a single clinical syndrome. NIDDK researchers recently reported in a study of Pima Indians, however, that insulin resistance in this population is not directly associated with the occurrence of hypertension. Rather, it is believed that this clinical problem is the result of a different mechanism. To explore this further, the relationship is now being studied in Caucasians.

In another study, NIDDK and university grantees are attempting to identify a single gene that may be responsible for insulin resistance and Type II diabetes in Pima Indians. First, the scientists collected DNA from Pima Indian families with a multi-generational diabetic history. They are now using a research technique -- called genetic linkage analysis -- that will allow them to identify genetic irregularities in these families. If they are successful in identifying the gene, this information will permit early identification of those who carry the Type II diabetes gene, as well as enable scientists to adopt more carefully targeted prevention strategies.

Intramural researchers have also begun work at the genetic level to understand the mechanisms that regulate the number of glucose transporters in a cell. Glucose transporters are the highly specialized proteins that convey glucose from a cell's outer membrane into its cytoplasm for energy production. However, glucose transporter activity is often impaired in Type II diabetes. Moreover, at least part of the regulation of these proteins occurs through changes in gene expression. If these genetic studies are fruitful, drugs could be developed that enhance transporter activity in peripheral tissues. Thus, one critical cellular breakdown in Type II diabetes could perhaps be corrected.

In another area of investigation, NIDDK scientists are studying extremely insulin-resistant patients to extend scientific understanding of normal insulin receptor activity and diabetes-causing insulin receptor defects. For example, using a cloned insulin receptor gene, intramural scientists recently identified several mutations in patients with rare and very devastating forms of insulin resistance. Because of these mutations, the researchers found that the cell is unable to metabolize glucose at normal rates. Indeed, some of these mutations cause the cell to have too few receptors on its surface. As a result, the cell is unable to metabolize glucose at normal levels. Other mutations interfere with a receptor's ability to mediate the cell's response to insulin. When this happens, the cell does not respond adequately to insulin's signal to begin glucose uptake. Future studies will extend these findings to see how relevant the two mutations are to more common forms of diabetes. In addition, possible tests for these mutations would help health professionals screen the population for genetic risk.

Meanwhile, Institute scientists are also studying the development of glucose sensing activity in pancreatic beta cells, the cells that produce and secrete insulin. This sensory mechanism enables beta cells to know when glucose reaches a certain level in the blood, such that the appropriate amount of insulin is released. Since glucose sensing is the last mechanism to develop in beta cells and is one of the first mechanisms to deteriorate in diabetic individuals, NIDDK scientists hope their research will provide the fundamental knowledge that underpins future therapies to rejuvenate these sensors in Type II diabetics. Recently, in studies of glucose sensors in developing animals, the researchers found that potassium ion channels exist in beta cell membranes before glucose sensing activity develops. This indicates that subtle regulation of potassium permeability is a developmental step in glucose sensing. Further, the scientists discovered that cell-to-cell coupling, stimulated by the hormone prolactin, is an important factor in glucose recognition.

Endocrinology

Parathyroid Studies

NIDDK intramural researchers have intensely investigated the molecular parameters of familial multiple endocrine neoplasia type I, a genetic disease characterized by tumors of the parathyroids and other endocrine glands. Recently, they found a growth factor in blood that contributes to the disease. Although this factor is not yet purified, scientists have already established that it is very similar to another well-characterized growth factor. These investigators have also shown that parathyroid tumors develop in this disease through a "two-hit" process that inactivates both copies of a particular gene. Ongoing studies are aimed at isolating this gene, and understanding the relation between gene-inactivation and the release of a growth factor in this process. These investigations have important implications for patient care, as well as for understanding normal development and growth of endocrine tissues.

Osteoporosis

To gain insight into osteoporosis and other bone disorders, NIDDK scientists are studying vitamin D -- a steroid-like molecule that regulates many aspects of calcium metabolism -- and its mechanism of action. As a part of this research, the scientists have developed cell lines from patients with a rare form of vitamin D resistance, which results from mutations in the receptor that binds to and mediates the actions of vitamin D. Moreover, they have used these mutant cells to characterize the role of the vitamin D receptor in normal cells. Recent studies found that vitamin D can affect normal cells in ways different from other steroid hormones, which regulate the expression of specific genes in the cell nucleus. In addition to its slow nuclear effects, vitamin D also causes very rapid changes in cell behavior. Most interestingly, the cell receptors that mediate the rapid changes seem identical to those mediating the slow nuclear events.

Thyroid Disease

Thyroid hormone is an important factor in human growth and regulation. If, for instance, the thyroid produces abnormal levels of this hormone during early life, it can induce serious developmental flaws. In one such syndrome, called Generalized Thyroid Hormone Resistance (GTHR), thyroid hormone fails to interact properly with its cell surface receptor, causing it to circulate freely in the bloodstream at elevated levels. Without this hormone's necessary cellular action, irregularities such as mental retardation, hyperactivity and impaired growth may result.

Based on earlier NIDDK intramural research which indicated that GTHR is a familial syndrome that is tightly linked to a mutation in a specific gene, scientists recently developed special DNA probes to diagnose the disease prenatally and during early childhood. These probes will allow early institution of thyroid hormone therapy to prevent the devastating effects of this disease.

In another clinical study, researchers are studying patients with pituitary gland tumors -- abnormal tissue growths that cause the secretion of an excess amount of thyroid hormone. Because the pituitary gland is attached to the base of the brain, these patients typically require treatment for both a brain tumor and hyperthyroidism. Moreover, these tumors can metastasize dangerously throughout the body, and have proven difficult to cure with conventional therapy. NIDDK scientists are now giving study patients a new synthetic version of the anti-hormone secreting protein somastatin, called octriotide, to control these tumors. The researchers report that in many cases this treatment has resulted in a cessation of tumor growth.

Metabolism

Cystic Fibrosis

Currently, physicians have no simple method to determine objectively the relative health of cystic fibrosis (CF) patients. However, NIDDK scientists recently found that measuring the level of the large glycoprotein, mucin, in a CF patient's blood may provide this information. Mucins protect against bacterial infection; for example, these glycoproteins bind to bacteria in the respiratory tract where ciliated epithelial cells later brush them away. With CF patients, however, secretory ducts become clogged and mucins leak into the blood. The researchers have shown that high mucin levels indicate that the health of a CF patient is deteriorating; a low mucin level reveals that the patient is relatively healthy. Interestingly, mucin levels may also provide an inexpensive method to test the effectiveness of CF drug therapies.

Tay-Sachs Disease

For many years, scientists believed that the infantile form of Tay-Sachs Disease -- a lethal metabolic disorder found most frequently in Ashkenazi Jews and French Canadians -- was caused by a single genetic mutation. NIDDK scientists, however, proved that was not the case. They recently cloned defective genes from Ashkenazi Jewish patients, and identified two different mutations. The first mutation arises when four nucleotides are incorrectly inserted into a specific gene. This mistake shortcircuits the production of the important cellular enzyme, beta-hexosaminidase, causing waste products to accumulate in the cell and subsequent nerve degeneration. It is estimated that this newly identified mutation accounts for 70 percent of all Ashkenazi carriers of the infantile form of the disease. In the second mutation, one nucleotide is substituted for another, thus cancelling the production of beta-hexosaminidase. Approximately 30 percent of all Ashkenazi carriers have this mutation. These findings are important because they will allow more accurate and informative genetic screening of the disease.

Like infantile Tay-Sachs, adult Tay-Sachs disease is found almost exclusively in Ashkenazi Jews. But, in the rarer, adult variety, the disorder occurs in the second or third decade of life and leads to mental decline rather than death. Nevertheless, adult Tay-Sachs disease is also caused by an accumulation of cellular waste products that leads to progressive nerve degeneration. Recently, an NIDDK scientist identified the exact mutation that causes adult Tay-Sachs disease. The researcher found that the disease results from a single substitution in the gene encoding for the beta-hexosamindase enzyme, the same enzyme that is affected in the infantile form. This finding is significant because it now allows for more specific genetic screening for the disease.

In a related study, NIDDK scientists found that Ashkenazi Jews suffering from adult Tay-Sachs disease carry one adult Tay-Sachs gene, and one juvenile Tay-Sachs gene. Interestingly, the infantile mutation appears in about 1 in every 30 Ashkenazi Jews, while the adult mutation occurs much less frequently. For this reason, the odds are genetically overwhelming that an adult mutation will be coupled with a infantile mutation in the Ashkenazi Jewish population. These new insights may eventually prove useful in combatting different forms of the disease.

Digestive Diseases

Obesity

One of the strongest risk factors for noninsulin-dependent diabetes is obesity. In fact, about two-thirds of all noninsulin dependent diabetics are obese when they are diagnosed with the disease. As a result, several NIDDK laboratories are now taking a special interest in learning more about the causes of obesity. At the NIDDK Phoenix Clinical Research Center, for example, researchers are using a highly sophisticated respiration chamber to measure energy expenditure in Pima Indians, a tribe with an extraordinarily high rate of obesity and diabetes. From this ongoing study, several important risk factors have been identified as contributing to the development of obesity. Most significantly, the researchers have substantiated that obesity is a familial trait that may be genetically determined. This finding is of considerable importance because it discounts the long-held belief that obesity results solely from inactivity or a behavioral shortcoming. The Phoenix researchers report that a slow metabolic rate (rate of conversion of food into energy) is also a risk factor for obesity. In fact, the slower a person's 24-hour metabolic rate, the more prone he or she would be to weight gain.

In a new study, the Phoenix scientists are utilizing a unique research approach that allows them to measure energy expenditure during a person's normal daily activity. Until recently, this data could only be collected in an artificial environment, such as the previously mentioned laboratory respiratory chamber. With the new technique, volunteers drink a glass of water containing a very small number of specially labeled water molecules. As each study participant goes about his or her daily activities, the researchers periodically sample body fluids from them to determine the presence of labeled carbon dioxide and hydrogen, the metabolic breakdown products of the labeled water. Using this technique, the researchers are able to measure carbon dioxide production to assess a person's rate of energy metabolism. Thus, NIDDK researchers will be able to more accurately study energy expenditure, as well as determine what role abnormal metabolism plays in the development of diabetes and obesity.

Liver Diseases

Hepatic encephalopathy is a neurological complication of liver failure that is characterized by mental confusion, or even coma. Each year, over 30,000 Americans die of liver disease because their physicians have difficulty treating them while they recover from hepatic encephalopathy. Recently, however, NIDDK researchers discovered a neural process that may be responsible for the syndrome. It occurs when elevated levels of naturally occurring sedatives, called benzodiazepines, increase in the brain and peripheral tissues, thereby depressing brain function and causing confusion or coma. This finding indicates that an effective means of correcting hepatic encephalopathy would be to treat patients with drugs that block benzodiazepine receptors -- the molecules to which benzodiazepine attaches for activation. In this way, the depressive effects of too much benzodiazepine could be rapidly reversed. In preliminary European clinical studies, where benzodiazepine receptor antagonists are now used therapeutically, this strategy has proven effective. In fact, nearly 80 percent of patients treated with these compounds had aspects of their hepatic encephalopathy reversed.

In important studies with recombinant alpha interferon, a naturally produced anti-infection protein, NIDDK researchers reported recently that they successfully treated half of their patients with chronic non-A non-B hepatitis (also known as Type C). This is a significant therapeutic step because it is the first time a drug has proven effective against this, the major form of hepatitis. Type C hepatitis, which is often transmitted by exposure to blood and blood products, accounts for over 90 percent of post transfusion hepatitis, and as great as 35 percent of sporadic viral hepatitis. Each year, approximately 75,000 Americans develop chronic Type C hepatitis, resulting in permanent and potentially life-threatening liver damage. To further enhance the benefits of alpha interferon, researchers are now preparing to combine the compound with one of two antiviral agents, ribavirin and dideoxyinosine. The latter compound is especially interesting because it was recently developed by NIH AIDS researchers. This research is a good illustration of how advances in AIDS research are having an impact on other areas of scientific investigation.

Kidney Diseases

In the kidney disease associated with systemic lupus erythematosus, the immune system mistakenly attacks the kidney's filtering apparatus, called the glomerulus. This misguided assault, due to an abnormality of the immune system, results in massive excretion of protein in the urine. The resultant depletion of blood protein, in turn, is accompanied by fluid retention and marked elevations in blood lipids, particularly cholesterol. As a result, those afflicted face a troubling list of complications such as fluid retention and swelling, hypertension, atherosclerosis, and ultimately kidney failure. Although it is presently undetermined whether this syndrome can be therapeutically controlled, NIDDK researchers are now testing in humans two immunosuppressive drugs -- cyclophosphamide and cyclosporin A -- to treat one form of this disease. The new approach is designed to evaluate the relative effectiveness of these drugs, each having a different mechanism of action on the immune system abnormalities that cause this difficult chronic disorder.

In another line of research, NIDDK scientists have developed two mouse models with diseased kidneys closely resembling those found in human diabetics. With these models, the researchers now possess a valuable research tool to probe the biochemical and genetic defects underpinning diabetic renal disease, a potentially lethal complication of diabetes that may be caused by hypertension in the kidney. In future studies, the researchers plan to investigate the factors regulating the production of the scarred connective tissue that is a hallmark of the kidney disease of diabetes.

Sadly, diabetic kidney disease is quite prevalent among all Native Americans, afflicting four times as many of them as Caucasians; and much higher rates are seen in some tribes, such as the Pima Indians. During the next several years, NIDDK researchers will apply a series of renal function tests to a group of diabetic Pima Indians to trace the natural history of diabetic nephropathy. This landmark study should provide much more definitive evidence of the cause and developmental factors of this disease.

Hematology

Sickle Cell Anemia

Sickle cell anemia is a potentially lethal hereditary disorder that is found almost exclusively in blacks. Research has shown that a gene mutation resulting in a single amino acid substitution produces the defective hemoglobin and abnormally shaped red blood cells characteristic of this disease. Because sickle cell anemia patients produce vast amounts of sickled hemoglobin, the disease is extremely difficult to treat. But, NIDDK researchers, in a joint clinical study with investigators from the National Heart, Lung and Blood Institute and The Johns Hopkins University Medical School, recently found that the drug hydroxyurea activated fetal hemoglobin genes in most of the severely affected sickle cell anemia patients who were treated. Fetal hemoglobin, which is the form of hemoglobin found in all individuals before birth, protects sickle cell patients from the effects of their abnormal hemoglobin until their first year of life. The clinical study's finding is significant because increased fetal hemoglobin production reduces the manufacture of harmful adult hemoglobin in sickle cell anemia patients. These researchers have recently shown that the levels of elevated fetal hemoglobin being achieved in most patients are high enough to give hope of some clinical benefits without significant toxicity. Controlled clinical trials are now being planned with this new treatment, as well as some variants on this approach that may give higher levels of fetal hemoglobin.

Neuroscience

Depressants

Many patients who undergo minor surgery, but receive general anesthesia, say that they would like to awaken soon after the procedure is completed. But because of the soporific action of general anesthesia, this is not physically possible. NIDDK researchers, however, recently reported that they were able in animal studies to reverse the effect of inhalation anesthesia by administering a specially designed synthetic compound. This agent acts to block the anesthetic from binding at the brain's benzodiazepine/GABA receptor complex -- a conglomeration of proteins that contain numerous recognition sites for psychopharmacological drugs. As a result, the sleep-producing effect of the anesthetic is shortened. If future tests are successful, this agent may prove effective in enabling patients to awaken sooner after surgery or other conditions in which inhalation anesthesia is used.

Opiates

A newly developed synthetic opiate compound, unnatural etorphine, has been found to be three times more potent as a cough suppressant than natural codeine in animal studies. Importantly, the researchers indicate that unnatural etorphine triggered no narcotic activity in test animals because it does not bind to opiate receptors. Rather, it is present in the brain as a "mirror-image" of its natural counterpart. This finding is significant, because codeine cough-suppressant preparations are currently the most effective available. However, they produce narcotic effects, such as intense drowsiness, and even stupor, and physicians generally will not prescribe codeine cough syrup for certain patients, including children. Unnatural etorphine could provide more effective cough suppressant therapy than is currently available, without the undesirable side-effects, if these preliminary results are confirmed and extended.

In a major collaboration with NIH clinicians, Institute researchers are comparing how the opiate receptor ligand, cyclofoxy, and the endogenous opiate receptor ligands called endorphins, affect the brains of normal individuals; and the brains of those who suffer from disorders such as autism, narcotic addiction, schizophrenia, and eating and sexual disorders. This is being done with Positron Emission Tomography (PET), a technique that allows investigators to visualize and monitor fluorine-labeled opiate molecules as they circulate and bind to their receptors in the brain. The researchers now plan to quantitate the brain's normal opiate receptor density. Then, based on the receptor density count, they hope to establish the biochemical basis of opiate receptor-associated disorders. If successful, this investigation would also provide a biochemical measure of the effects of drug therapy in the brain, and would mark an important diagnostic advance, because psychologists now have only empirical methods to diagnose these problems.

Stroke

Researchers now believe that, when stroke occurs, oxygen and other essential cellular nutrients are blocked from the brain, thereby triggering an excessive release of the amino acid glutamate. This action causes large and harmful accumulations of calcium in brain cells. When applied to test animals in a timely manner, PCP-like compounds reduce calcium flow into the affected brain cells, allowing them to recooperate much more rapidly and with little or no serious injury. Using computer-generated models, Intramural researchers have now determined the minimum molecular requirements for creating phencyclidine (PCP)-like compounds. With this molecular blueprint in hand, they will better be able to modify structurally the basic PCP nucleus and control the pharmacological properties of the resulting compounds in order to develop more highly targeted synthetic PCP drugs for use in stroke patients.

Biotechnology

Transgenic Mice

Transgenic animals are unique models for studying how genetic regulatory elements control gene expression. These animal models may one day provide the scientists with the knowledge to control the switches that turn genes on and off. With the U.S. Department of Agriculture, NIDDK scientists recently developed transgenic pigs that had a gene for a specific mouse milk protein spliced into their DNA. During lactation this protein was secreted into pig milk. Thus, scientists demonstrated the possibility of converting the mammary glands of farm animals into bioreactors, producing milk with an altered protein composition. This technology, which was originally developed by NIDDK and NICHD scientists in a mouse model system, can now be used to synthesize pharmaceuticals and other valuable proteins in the milk of farm animals, like cows and sheep. The desired proteins can then be extracted in large quantities from the animals' milk.

Conception

Intramural scientists are attempting to "regulate fertility" -- to provide therapeutics for infertile couples and vaccines to prevent conception. They have cloned three genes that code for proteins of the coat surrounding egg cells and early embryos. Using cloned DNA and a previously described contraceptive monoclonal antibody, these investigators have identified an egg cell coat peptide to test as a contraceptive vaccine. Female mice immunized with this peptide develop antibodies that bind to the egg cell coat, preventing fertilization. In a recent study that may have application to humans, 70 per cent of these mice were infertile -- with the effect being reversible in half. In the near future, these researchers will use transgenic mice to investigate further the genetic controls of egg cell and egg cell coat development. By learning more about the molecular details of fertilization, these researchers also hope that they will ultimately be able to produce better therapeutics for infertile couples.

Rationale for the Budget Request:

The FY 1991 request for Intramural Research is $73,295,000 and an employment level of 439 FTEs. This is an increase of $4,567,000 and 11 FTEs over the FY 1990 levels of $68,728,000 and 428 FTEs.

National Institute of Diabetes and Digestive and Kidney Diseases

Research Management and Support

Authorization: Indefinite.

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
175	$19,916,000	179	$20,698,000	+4	+$782,000

Purpose and Method of Operation

Support is provided through this activity for the immediate office of the Institute Director and for certain administrative and business management functions including financial management, personnel management, property control, and travel audit and control, which are most efficiently performed as centralized functions. Staff continues to assume new responsibilities and reporting functions such as those required under the manpower productivity measurement program and the Freedom of Information Act.

A major portion of the resources of this activity is devoted to review and approval of grants functions, including professional and support personnel who are responsible for the administration of the Institute's grants activities. The staff assists in the planning and development of programs in research, training, and fellowships that will best serve to accomplish the desired results in the areas of disease interest for which this Institute is responsible; reviews and evaluates research and training grant applications for presentation to the NIDDK Advisory Council and provides required Council staff assistance; serves as liaison with applicants, grantees, other components of NIH and the Department, advisory bodies, and interest organizations; and provides continuous surveillance of scientific information relevant to all transactions.

Other functions included under this activity are the review, management and negotiation of research and development contracts of the categorical program areas, and support of the three national advisory boards in diabetes, digestive diseases, and kidney and urological diseases.

Rationale for the Budget Request:

The FY 1991 request for Research Management and Support is $20,698,000 and an employment level of 179 FTEs. This is an increase of $782,000 and 4 FTEs over the FY 1990 levels of $19,916,000 and 175 FTEs.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Detail of Permanent Positions

	1989 Actual	1990 Appropriation	1991 Estimate
ES-61	15	15	15
ES-60	5	5	5
ES-00	4	4	4
Subtotal	24	24	24
GS/GM-15	44	44	44
GS/GM-14	47	47	49
GS/GM-13	33	33	35
GS-12	37	37	40
GS-11	32	35	36
GS-10	1	1	1
GS-09	29	31	31
GS-08	23	23	23
GS-07	51	51	55
GS-06	23	23	23
GS-05	17	17	20
GS-04	10	10	10
GS-03	2	2	2
GS-02	0	0	0
Subtotal	349	354	369
Grades established by act of July 1, 1944 (42 U.S.C. 207):			
Surgeon General Grade	0	0	0
Assistant Surgeon General Grade	2	2	2
Director Grade	23	23	23
Senior Grade	3	3	3
Full Grade	1	1	1
Senior Assistant Grade	1	1	1
Subtotal	30	30	30
Ungraded	8	8	8
Total permanent positions	411	416	431

National Institute of Diabetes and Digestive and Kidney Diseases

New Positions Requested

NIDDK Intramural Research	1991 Grade	 Number	 Annual Salary
Research Chemist....................	GS-14	1	$46,679
Research Chemist....................	GS-13	2	79,002
Research Biologist..................	GS-12	1	33,218
Biological Laboratory Technician....	GS-07	4	74,907
Purchasing Agent....................	GS-05	3	27,026
		11	260,832

NIDDK Research Management and Support	Grade	Number	Annual Salary
Health Scientist Administrator......	GS-14	1	46,679
Grants Management Specialist........	GS-12	2	66,436
Grants Management Specialist........	GS-11	1	27,716
		4	140,831

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Advisory and Assistance Services

For 1991, the Advisory and Assistance Services budget will be $297,000, an increase of $12,000 over the 1990 level of $285,000. These funds are used primarily to support two program aspects: appointed positions mandated by law for the NIDDK Council, Board of Scientific counselors, and three national advisory boards; and ad hoc consultants from the non-government communities who provide programmatic advice to Institute staff during workshops, conferences, hearings, etc. and represent fresh, independent points of view to provide extramural program direction. Institute staff do not perform these services either because of conflicts with legal mandates or because of need for more specific programmatic expertise.

The majority of the Institute expenditures in the AAS categories are for many relatively small purchase orders written for our consultants. The amounts are to cover travel, per diem and modest honorariums. Internal controls begin with careful screening by Institute administrative officers to ensure compliance with regulations and separate accounts are designated for recording advisory and assistance services obligations. In addition, during the course of the year, each of the administrative officers is audited by an NIH team and the purchase orders for the consultants are screened.

WEDNESDAY, MARCH 14, 1990.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

WITNESSES

DR. MURRAY GOLDSTEIN, DIRECTOR
DR. WILLIAM F. RAUB, ACTING DIRECTOR, NIH
DR. W. WATSON ALBERTS, ACTING DEPUTY DIRECTOR, NINDS
RICHARD L. SHERBERT, EXECUTIVE OFFICER, NINDS
ANDREW C. BALDUS, BUDGET OFFICER, NINDS
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. NATCHER. We take up next the National Institute of Neurological Disorders and Stroke.

We have before the committee at this time Dr. Murray Goldstein. Dr. Goldstein, it's a pleasure to have you back before the committee; and before you give us your statement, tell us who you have with you there at the table.

Dr. GOLDSTEIN. Thank you, Mr. Chairman.

On my far left is Mr. Sherbert, the Executive Officer of the Institute.

Next to him, Dr. Alberts, the Acting Deputy Director of the Institute.

On my right, Mr. Baldus, who is the Budget Officer of the Institute.

You know the other members at the table.

DECADE OF THE BRAIN

Mr. NATCHER. Thank you very much.

Now, Dr. Goldstein, we would be pleased to hear from you.

Dr. GOLDSTEIN. Thank you, Mr. Chairman.

As you and this committee know so well, this is the first year of the "Decade of the Brain," and within this first year, we expect to accomplish a great deal. My written report documents these goals for you, both in terms of specific areas and the contribution we can expect from basic and clinical research.

Let me inform you about an expert committee which has been organized to draft the NINDS implementation plan for the Decade of the Brain. It is a panel of 10 persons, eight of whom are scientists, two of whom are lay people. The Panel has had its first meeting.

It will have its second meeting in April, calling upon the public to testify before it in regard to needs and opportunities to solve the problems of neurological disease. The NINDS National Advisory Council will send this committee on June 1 an implementation plan for the decade, so that you will know specifically what the scientists and the people of this country are asking of us and the reality of achieving those goals.

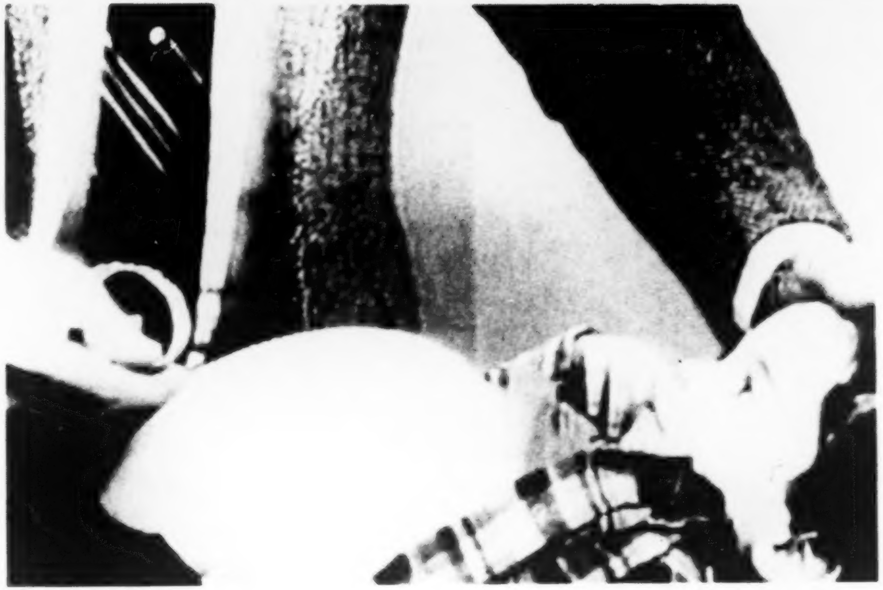
GAUCHER'S DISEASE

In the time available, I will try to discuss two research issues which I hope will be of interest to you. Twenty-five percent of all human genetic disorders are disorders of the nervous system. To date, there has not been a treatment available for any neurological genetic metabolic disorder; that is, until last month.

We now have had a breakthrough, and we have a treatment for a genetic metabolic disorder. Let me show it to you.

[Chart follows:]

Patient with Gaucher's Disease Before Treatment

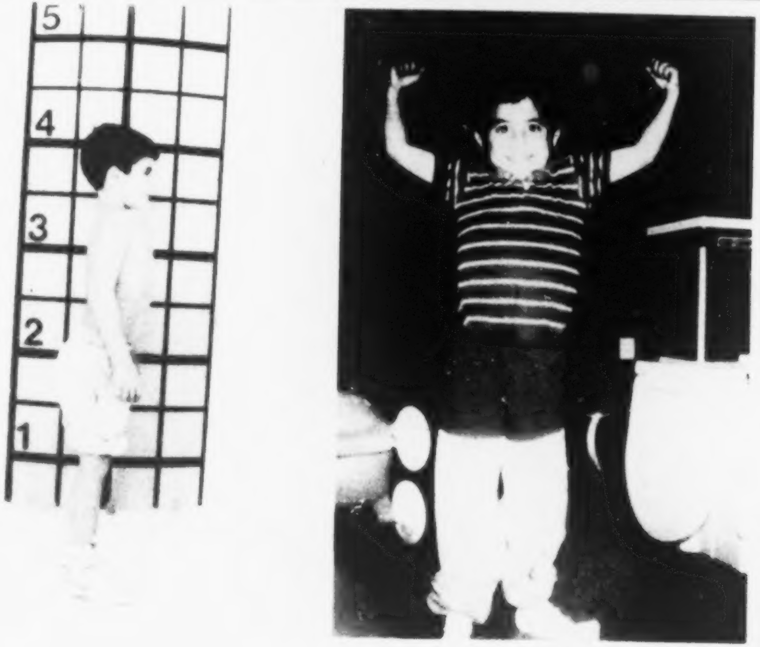


Mr. Chairman, this photograph is that of a child with Gaucher's disease. You will notice the abnormal size of this child's abdomen. The abdomen is not full of fluid; it is filled with the child's liver and spleen. His organs take up the entire abdominal area.

Gaucher's disease is a genetic disorder, and this child would have progressed first to mental retardation and then to death; that is until last month.

[Chart follows:]

Patient with Gaucher's Disease After Treatment



Let me show you that child last month. This is a dramatic example that medical research does pay off. Thirteen children are now under active research therapy at the NIH Neurological Institute. When this remarkable result occurred with the first child, we didn't believe it. We thought it was some kind of fluke of nature. But we now have 13 afflicted children who are beginning to make similar improvements.

Let me emphasize one. This is a treatment, it is not a cure. This is enzyme replacement therapy. This child, because of a genetic defect, was not able to produce the enzyme necessary to rid his body of the waste products of his own metabolism.

We discovered in our NINDS laboratories in Bethesda what that enzyme deficiency was; and for 8 years, we have tried to perfect the production and administration of that enzyme so that when given to this child, this clinical result would occur.

We have finally done that. Our next steps in this research will include determining what the lowest minimum dose of enzyme is this child will need to maintain him.

Secondly, what is the long-term effect? Will this beneficial effect decrease in a year or two? The long term beneficial effect of enzyme therapy is obviously what we still don't know.

The final step, of course, is not to treat this child, but to cure the child. As you have discussed with other Institute directors, that procedure is genetic engineering, introducing the missing gene into the child so he can make his own needed enzyme.

We are now hard at work on achieving that objective. But I did want to bring this breakthrough in therapy to your attention, because it does highlight what we can expect of neurological research in the "Decade of the Brain."

We have made our first breakthrough in enzyme replacement therapy for a neurological genetic disease. Hopefully, the template which has been established in terms of delivering this form of therapy will also serve as a foundation for the treatment of other genetic diseases as we discover the enzymes needed and develop the specific methodologies of their administration to the patient.

And so, sir, I am very proud of this NINDS accomplishment. Our laboratory scientists at NINDS are obviously to be complimented.

ACUTE BRAIN INJURY

The next area I would like to share with you is something we haven't yet accomplished, but we are getting close.

Two of the major diseases that our Institute is faced with involve acute injury to the brain, acute stroke and acute head injury.

The important issues are, how to intervene and when to intervene to protect the threatened brain.

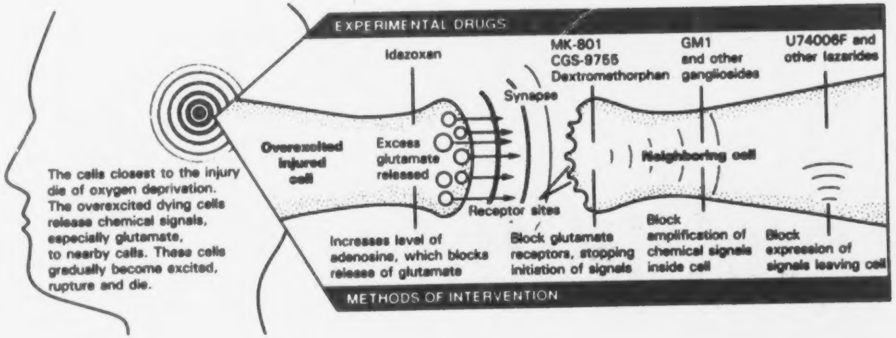
To date, most research has been at the two temporal extremes. First, to prevent the brain injury, which is still the most important objective. We must protect the brain from injury.

The other is after the brain has been injured, what to do to return its function. Unfortunately, we have not had a good strategy on what do to while the brain was being damaged; namely, within the first 20 minutes to 4 hours. Could we do for the brain what our heart colleagues have done for the heart; namely, protect it during the acute period of injury, and intervene rapidly and effectively to make sure the damage doesn't progress?

[Chart follows:]

Interrupting a Cascade of Cell Death in the Brain

Scientists are experimenting with drugs to interrupt the chemical chain reaction that spreads cell death after a stroke.


EXPERIMENTAL DRUGS
Idazoxan
MK-801
CGS-9755
Dextromethorphan
GM1
and other
gangliosides
U74006F and
other lazarides
Synapse
Overexcited
injured
cell
Excess
glutamate
released
Neighboring cell
Receptor sites
Increases level of
adenosine, which blocks
release of glutamate
Block glutamate
receptors, stopping
initiation of signals
Block
amplification of
chemical signals
inside cell
Block
expression of
signals leaving cell
METHODS OF INTERVENTION

The cells closest to the injury die of oxygen deprivation. The overexcited dying cells release chemical signals, especially glutamate, to nearby cells. These cells gradually become excited, rupture and die.

Copyright© 1989 by The New York Times Company. Reprinted by permission.

This interesting chart was published in the New York Times. They did such a good job, we asked them for permission to show it to you. What this illustrates is a nerve cell which has just been damaged. Imagine this nerve cell is in the brain and the damage is due to stroke or head injury. We are unraveling what happens. For example, an excitatory amino acid, a substance that is normally produced by the cell and released in small quantities all the time, is suddenly released in large amounts due to an injury. It floods the next cell, and essentially puts the next cell into high gear, burning it out metabolically.

If we can intervene before the damage is done, before the burnout occurs, we can stop the further development of the stroke. We can stop the progression of the damage to the brain due to head injury. The few cells that were killed initially are no longer joined by the thousands of other cells that get caught up in the damage due to the release of the injured cell's excitatory amino acid.

The drawing illustrates examples of the drugs which may be useful at different stages of the cells deterioration that are presently under study. We don't know which one of these will work, and it could very well be a combination of them will be needed, somewhat like chemotherapy for cancer.

When we stop the damaged cell from releasing the excitatory amino acid, should we prevent the cell right next to it from picking it up, or should we intervene in the metabolism of the cell to protect it from overactivity, or do we do both? The important point is we now have experimental methods to explore how to protect the threatened brain.

This, Mr. Chairman, is where we are trying to go in acute intervention for acute stroke and for acute head injury. In the interim, research on restitution of function, including rehabilitation, continues to be an important research priority of the NINDS.

Mr. Chairman, I hope my written document describes where we are at the moment and, what our goals and objectives are. The President's budget request for our Institute for fiscal year 1991 is $512,212,000.

Thank you, sir.

[The prepared statement of the Director, National Institute of Neurological Disorders and Stroke follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute of Neurological Disorders and Stroke

This year the National Institute of Neurological Disorders and Stroke (NINDS) celebrates 40 years of neurological and neuromuscular research conducted and supported by the Institute in its own laboratories and clinics and in other institutions across the United States and around the world. Since 1950 the Institute's efforts have contributed to steady progress in understanding, preventing, and treating the hundreds of neurological disorders that threaten and impair the quality of life of millions in this country and elsewhere. When NINDS was created only two neurotransmitters--the substances by which nerves talk to each other--were known to exist; today over 40 substances are known to be involved with neurotransmission, many of them found in just the last 10 years. In 1950 the standard of brain imaging was an X-ray; today we can chart the electrical, magnetic, biochemical, and metabolic landscape of the cortex and deeper brain structures. Just 10 years ago we could only observe and chart the nerve damage caused by trauma or degeneration; now we know that damaged neurons can regrow and transmit impulses again and we are acquiring the tools to reduce or halt the progression of disease symptoms. Progress in the application of genetics, biotechnology, and new surgical approaches has been similarly dramatic.

The Congress and the President recognized the impact of neurological diseases on millions of Americans and expressed their belief in the potential of neurological research for even greater progress by designating the decade beginning January 1, 1990 as the "Decade of the Brain." This call for even greater effort on the part of the government and the public offers a unique opportunity for addressing the research, medical, and behavioral issues related to the human brain and its functions.

During this decade, the NINDS will continue to lead the national effort in neurological and neuromuscular research and research training. The labors of that mission have resulted in amazing discoveries: how nerve cells receive and transmit information; how the nervous system is organized and allows us to perceive, learn, and act; how viruses, the immune system, and defective genes create neurological disease; and, most importantly, how we can intervene with surgery, medication, or lifestyle changes to prevent, alleviate, or cure many neurological and neuromuscular diseases and disorders. We have made significant, but still only early progress in understanding stroke, multiple sclerosis, Parkinson's disease, rare neurogenetic diseases such as lipid storage diseases and neurofibromatosis, muscular dystrophy, and head and spinal cord injury.

Much has been accomplished--so much more remains to be done. The designation of the "Decade of the Brain" expresses the belief that past discoveries will lead to even greater achievements. I assure you that this belief is well-founded.

For the first time, we have evidence of a drug that can slow the progression of a neurodegenerative disease. Patients with early Parkinson's disease are being treated with deprenyl and/or tocopherol--a component of vitamin E--in a clinical trial supported by NINDS. Previous studies in an animal model of Parkinson's disease suggested that highly reactive free radicals (chemicals produced by metabolic reactions) could be responsible for some of the nerve cell loss found with the disease. Tocopherol can "soak-up" free radicals after they are formed and deprenyl can prevent their formation. The effectiveness of deprenyl was clearly confirmed by early results of the clinical trial; deprenyl delayed by many months the need for traditional antiparkinsonian treatment, which can have side effects and limited efficacy. For those patients, this meant more months of working and living a normal life. The results were so clear that the study directors took the unusual step of publishing the results from the study before its completion so that the findings could be disseminated to the medical community and patients could begin to benefit from the trial. Additional studies will elaborate on the long term utility of deprenyl and tocopherol in treating Parkinson's disease.

These findings represent a major breakthrough for Parkinson's disease patients and raise important questions about the applicability of the finding to other neurodegenerative diseases, such as Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis. We expect that this will be a lively area of research for the next several years.

Over the next decade, NINDS scientists and grantees can be counted upon to continue to make progress in finding disease-causing genes and genes that regulate normal components of the nervous system, as well as expanding our understanding of the genetic basis of nerve function. A technological breakthrough promises to further expand the potential of neurogenetics research. Scientists can now introduce genes into non-dividing cells--such as neurons--and obtain expression of those genes, thereby opening the way for new studies of neuronal growth and function. Particularly promising are efforts by intramural and extramural scientists to pinpoint the genes for Huntington's Disease and neurofibromatosis.

When a gene responsible for a disease is identified, a logical next step is to characterize the gene product whose abnormality may result in clinical disease. Such discoveries lead to the possibility that molecular genetics may be applied to the development of clinical treatments. For example, scientists have recently transplanted normal muscle precursor cells into animals genetically deficient for dystrophin, the normal protein which is absent or defective in Duchenne muscular dystrophy. The transplanted cells fused with the deficient muscle fibers and produced dystrophin. In a different animal model, treated dystrophic animals showed improvement in their symptoms and lived longer than untreated dystrophic animals. Preliminary steps are underway to develop the cell transplant technique for potential application in human patients. The cure for muscular dystrophy is in the offing.

Increased understanding of the genetic mechanisms of neurological disease allows us to work toward immediate and long-term strategies. For instance, while intramural scientists continue to make significant progress in enzyme replacement therapy for Type I Gaucher's disease, they are also working on a more fundamental treatment using gene replacement techniques. The scientists have inserted the human gene for the enzyme missing in Gaucher's disease into mouse bone marrow, which then produced the enzyme, human glucocerebrosidase. Additional work must be done before determining the utility of this technique in humans; but if successful, clinicians would have a method to treat Gaucher's disease that could permanently alleviate the disease. In another example, data from the NINDS-supported Huntington's Disease Roster show that children of affected fathers develop the disease at a much earlier age than children of mothers with HD. It is theorized that the mechanism is a chemical change imposed on the Huntington's disease gene. If so, this may present an opportunity to intervene and "turn-off" the gene and delay the onset of disease.

We have in place a framework of epidemiologic studies, clinical trials, and laboratory investigations to tackle stroke, this nation's third leading killer and a major cause of disability. Stroke affects all segments of the population. Stroke incidence is now again rising, but we don't know why. Even low birthweight infants suffer mortality and morbidity resulting from brain hemorrhage. We are looking forward to the results of an NINDS-supported trial to test the efficacy and safety of a drug called indomethacin to prevent brain bleeding in these infants. Two ongoing studies in minority populations are expected to reveal clues about the greater occurrence of stroke in minority groups; more studies of this nature are being sought.

One of the key research issues in stroke over the next decade will be the medical management of patients while stroke is occurring. Much of the injury occurs over several hours when tissues die as a result of lack of oxygen and the cascade of physiologic effects that follow. Interventions under study include the regulation of hydrogen ions, alteration in brain temperature, inhibition of excitatory amino acids, and regulation of blood flow to damaged tissues. Blood sugar levels have also emerged as a factor in the occurrence of silent stroke, transient ischemic attacks that often precede a major stroke, and tissue damage following a stroke. Better medical management will mean the difference between someone who returns to the activities of daily living versus someone who is left paralyzed or speechless and dependent on family and health care services to survive.

Surgical and medical strategies have greatly improved the outlook for people with epilepsy. There remains, however, a core of patients whose seizures are not controlled--they have more than one seizure a month--even with state-of-the-art treatment. To help these people, NINDS grantees and intramural scientists are working on a two-pronged attack to screen drugs for their anti-epileptic potential and to understand the physiology of how nerve cells fire. Knowing how nerve cells are regulated will lead to improved medications to stop nerve cells from firing in the uncontrolled, explosive manner characteristic of seizures.

Amyotrophic lateral sclerosis (ALS, or "Lou Gehrig disease") is the best known of the motor neuron diseases. These disorders have been particularly resistant to efforts to identify a causative factor or therapeutic agent. Though the pathogenesis remains unknown, investigators are encouraged that we now have the tools and methodologies to mount more targeted investigations of the motor neuron degeneration characteristic of ALS. For instance, advances in neurobiology provide the means to study the role of neurotransmitters, their receptors, and nerve growth factor. Further clues to the disease are expected to come from the study of the structure and function of the affected nerve cells and tracts as well as genetic factors which can be found in relation to the disease.

The devastating effects of AIDS are particularly apparent in the nervous system. Some 30 percent of AIDS patients experience neurological complications early in the course of their illness; more than 70 percent suffer from neurological problems as the disease progresses. Recent findings indicate that the viral material in neuro-AIDS differs from that in patients who do not exhibit neurological involvement. Examining the mechanism and implications of this phenomenon is a high priority.

Head injury is the leading cause of death and disability in children and young adults. In addition, each year 10,000 to 12,000 Americans are disabled by trauma to the spinal cord. Though we are still working towards complete understanding of the mechanisms of trauma to the nervous system, we have exciting leads for the development of treatment strategies.

Underlying the advances I have described here--and the source for emerging clinical treatments over the next decade--is a vigorous intramural and extramural research agenda in the basic neurosciences. Studies in neurophysiology and neurochemistry will be the wellspring of potential therapeutic agents. Scientists are seeking mechanisms to allow drugs to cross the blood-brain barrier more easily and get to where they are needed in the brain. Further elucidation of the metabolic and cellular events responsible for tissue damage--due to stroke, traumatic brain injury, spinal cord injury, and epilepsy--will be facilitated by advances in tissue culture systems. The exploration of nerve growth factors and the conditions necessary to encourage and guide nerve cell growth and repair will contribute to methods of restoring nervous system functions. Developmental neurobiology studies demonstrate that cell-to-cell interactions are important for regulating growth of glial cells; these findings feed directly into understanding of the formation and growth of neural tumors. Insights into neurotransmitters and the coordination of neural networks will expand our understanding of learning disabilities, autism, sleep disorders, and normal cognitive functions such as learning and memory.

The neurosciences are on the verge of a new era. The consensus in the scientific community is that, amazing as past discoveries have been, they are truly only a glimpse of what we can expect throughout the "Decade of the Brain" from both basic neuroscience discoveries and clinical neurological research.

Mr. Chairman, the FY 1991 budget request for this Institute is $512,212,000. I am pleased to answer any questions you might have.

DOWNWARD NEGOTIATION

Mr. NATCHER. Thank you, Dr. Goldstein.

Doctor, your 25 percent downward negotiation rate for new grants is the largest at the National Institutes of Health. Why did you decide on this rather than reducing the number of new grants?

Dr. GOLDSTEIN. Mr. Chairman, that proposal is not our plan. We are not proposing to cut grants 25 percent.

We are cutting grants an average of 12 percent this year. We are not cutting them 25 percent.

Mr. NATCHER. Well, now, Doctor, some of the records that you have sent to the committee, don't these records show a 25 percent downward negotiation?

Dr. GOLDSTEIN. I am sorry, Mr. Chairman, I don't know which tables you are looking at. However, I can tell you, sir, we are now cutting grants an average of 12 percent and propose to do the same next year.

Mr. NATCHER. When we get the transcript back now, Doctor, go a little more into detail on that. We would appreciate it.

[The information follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

National Institute of Neurological
Disorders and Stroke
Bethesda, Maryland 20892
Building: 31
Room · 8A52
(301) 496-9746

March 30, 1990

To: Chairman, House Subcommittee on Labor, Health and
Human Services, Education
THROUGH: Acting Director, NIH W F Raub 30MAR90

From: Director, NINDS

Subject: Cuts in NINDS Competing Grant Awards for Fiscal Year 1991

Please allow me to elaborate on my recent testimony before the House Appropriations Subcommittee regarding the President's Budget for the National Institute of Neurological Disorders and Stroke for Fiscal Year 1991.

The NIH tables as presented to the Subcommittee accurately capture the original data that the NINDS provided to the Office of the Director, NIH, consistent with the guidelines established by that office. They correctly indicate that the NINDS would have to downward negotiate nearly all competing research project grants by 25 percent in order to award 405 competing grants within the resources the NIH has identified for research project grants in the FY 1991 President's Budget.

As I reviewed our allocation of FY 1991 resources for research project grants, I became concerned that downward negotiations of 25 percent from projected full study section recommended levels would prevent an investigator from fully meeting the objectives of an approved research project. I therefore intend to adjust the FY 1991 request for NINDS in order to reduce the downward negotiation rate on new and competing grants to 12 percent. This revision would result in a reduction in the number of new and competing grants supported in 1991 by 51, from 405 to 354. I believe it would be better to reduce the number of competing research project grants in 1991 in order to maintain the downward negotiation rate for each project at 12 percent.

In addition, NINDS also intends to reduce the number of new and competing grants in 1990 by 56, from 471 originally estimated to 415. The 1990 revision would limit downward negotiations to 12 percent in 1990 for new and competing grants. With the revised downward negotiations, the funded average cost for new and competing grants will increase from $170 thousand in 1989 to $203 thousand in 1990. The average cost for 1991 will be approximately $200 thousand.

My comments made during the hearing regarding the NINDS downward negotiation rates were made with these budget revisions in mind. Again, the NIH tables indicating a 25 percent downward negotiation rate are correct in that awarding 405 competing grants would require reductions of this magnitude. However, as stated above, the NINDS now proposes to fund 354 competing research grants at a downward negotiation rate of 12 percent. Appropriate revisions to the FY 1991 Congressional Justification provided earlier to the Subcommittee will follow shortly.

I regret if my oral remarks resulted in confusion regarding the President's Budget.

Murray Goldstein

Murray Goldstein, D.O., M.P.H.

RESEARCH PRIORITIES

Mr. **Natcher**. Now, assuming, Dr. Goldstein, that additional funds for your Institute become available, where would the priority be, the number of grants or the size of the awards? What would you do, Doctor, assuming that we could get additional funding?

Dr. **Goldstein**. We would invest our funds primarily in three targeted areas of research, maintaining the others, at a full level of effort.

Let me start by saying one of the first considerations we would give is to reducing the amount of individual project cuts. Over and above that, we would accelerate our newly designated and exciting effort in neurogenetic research; for example: neurofibromatosis, Huntington's disease, et cetera.

The second area we would target is head and spinal cord injury research. Every 15 seconds somebody is head injured in this country. Every 5 minutes somebody dies from a head injury. This research effort has got to be accelerated.

And the third area is clinical trials. After 40 years of generous support by this committee, and by the way, sir, this is our 40th anniversary, we now have enough information from basic neuroscience to vigorously enter the clinical trials area to further reduce mortality and improve the quality of life of patients with brain disease.

BALANCE BETWEEN GRANTS

Mr. **Natcher**. In how many more years, Doctor, do you expect your Institute to establish a new balance between continuing and new grants?

Dr. **Goldstein**. At the level of the President's budget, it would take 4 years, sir.

RESEARCH MANAGEMENT AND SUPPORT

Mr. **Natcher**. With the budget situation as it is, why does your research management and support request increase at a faster rate than extramural research, especially when you don't plan to hire additional staff, Doctor?

Dr. **Goldstein**. You mean the amount of funds for the administrative support of the Institute?

Mr. **Natcher**. Yes.

Dr. **Goldstein**. Sir, that is a formula allocation which is given to us. We, ourselves, do not develop it.

RESEARCH CENTERS

Mr. **Natcher**. Your funding for research centers, as you know, has been about the same, flat or declining slightly, for at least the past four budgets, Doctor. Have you considered reducing the number of centers so that an increase could be given to the remaining centers?

Dr. **Goldstein**. That decision is being discussed at the moment. We are cutting the budgets of our centers so badly that their viability and research productivity is really threatened. Our next step will be to reduce the number of centers so that we don't cut them any further.

Mr. NATCHER. How many of your centers will be up for re-competition in 1991?

Dr. GOLDSTEIN. Twenty percent, sir.

RESEARCH PRIORITIES

Mr. NATCHER. What are your two top or three research funding priorities for 1991, Doctor?

Dr. GOLDSTEIN. Neurogenetics research, head and spinal cord injury research, and clinical trials will receive our first priority attention. I am a little hesitant to say that because with all the other important areas of responsibility of the Institute, stroke, epilepsy, multiple sclerosis, ALS, I don't want to imply that we are not going to also have a vigorous program in each of these areas. What I am trying to identify is what would be three major areas of additional attention.

GRANT APPLICATIONS

Mr. NATCHER. Now, Doctor, excluding deafness research, the number of grant applications has been relatively flat for the past 5 years.

Is this unusual in a field that is advancing rapidly?

Dr. GOLDSTEIN. The problem we see is that when scientists come up for the second and third time, get approved and not funded, they are discouraged and leave research.

What we are facing now is a meaningful part of the scientific community leaving the research arena, saying they are spending too much time with no return.

The second problem we are facing, which in the long run is even much more dangerous, is that young people are terribly discouraged. They are now saying, why should I spend 12 additional years in training in order to obtain the necessary research skills. When I apply, I am not going to get my grant; even my professor cannot get his.

And so the long-term consequences may be more dangerous than the immediate.

JAVITS AWARDS

Mr. NATCHER. Dr. Goldstein, tell us why you are discontinuing the Javits investigator awards?

Dr. GOLDSTEIN. Sir, there are two Javits award programs—let me clarify that, if I may.

There are two separate programs of Javits awards. One is the Javits Investigator Award which we are not discontinuing. That is a viable, vigorous program which we will continue to support with great enthusiasm. It provides stable support to the finest investigators in neuroscience research.

What we are discontinuing are the Javits Centers of Excellence. Five years ago, this committee provided funds for this experimental new program for a 5-year period. That 5-year period has now ended.

These are research centers where the best of the brightest were given the opportunity not to do the kinds of research for which they would normally apply to NIH. Instead, to do the kinds of research that nobody would have the courage to apply for, jump over the technical boundaries and approach problems the solution to which will open completely new frontiers for the future. They are truly Centers of Excellence, Centers of Innovation. Four such awards were made.

They are now coming to an end, the period of commitment is over. Within our budget for fiscal year 1991, we cannot award four centers to replace these.

PET CENTERS

Mr. NATCHER. How much funding, Doctor, are you requesting for the PET centers in 1991?

Dr. GOLDSTEIN. Approximately $6,000,000, but I will correct that for the record, sir.

[The information follows:]

The NINDS serves as the Public Health Service focal point for PET research on the brain and spinal cord. This includes neurological disorders such as epilepsy, stroke and multiple sclerosis, as well as the dementia's (eg. Alzheimer's Disease), learning disabilities, drug and alcohol abuse, and neuropsychiatric disorders. The amount recommended for support of this program for fiscal year 1990 is $16.1 million; of this $11.0 million was provided. For fiscal year 1991, the recommended amount is $16.2 million of which $11.5 million can be funded. In addition, there is now a desperate need for updating the PET monitoring equipment which averages 10 years of age. The modernization of this equipment will require $10 million.

Mr. NATCHER. All right.

Tell us, if you will, how many PET centers would be supported compared to 1990 and what rate of downward negotiations would we have, Doctor?

Dr. GOLDSTEIN. In order to maintain the present seven PET centers in 1991, the research budget cuts will average between 25 and 50 percent per center.

FETAL TISSUE

Mr. NATCHER. Are there any substitutes available for fetal tissue for research using implants to treat diseases like Parkinson's disease, Doctor?

Dr. GOLDSTEIN. We think there may be. There are two non-fetal cell experimental implants that are presently being tested. One is to take the patient's cells—cells from the patient's own skin, fibroblasts, alter them genetically, so that they produce a chemical that is missing in the Parkinsons Disease patients brain called dopamine, and implant those cells from the patient into the same patient's brain. This has been done successfully in animals and is now being considered for human trial.

The second is a surprising lead which we are exploring in our own laboratories at the NINDS. We have found that cells from the placenta can produce the neurotransmitter materials that are missing.

In animals, we have now implanted placental cells into an animal brain that have been made Parkinson like. The preliminary results are very successful, and if this continues, as well as it appears to, within a year we will be doing implantation using placental tissue.

Mr. Natcher. Thank you, Dr. Goldstein.

Doctor, you know our subcommittee well; you have been before us on a number of occasions.

We are trying to help you, Doctor.

Dr. Goldstein. I understand, sir.

Mr. Natcher. You know, we believe in you and your Institute. You have heard me say that on more than one occasion.

Dr. Goldstein. I am very grateful.

Mr. Natcher. We want to bring out a bill that Joe Early will like. You know, he is our friend, Doctor. He and Mr. Stokes and Mr. Conte and all of us, we want to bring one out that you will like, Doctor.

You may not be able to brag about it in Dr. Raub's presence, but we want you to like it.

Dr. Goldstein. Mr. Natcher, I can assure you that any bill you like, I will like.

Mr. Natcher. Thank you, Doctor.

Mr. Conte, you try your hand.

COGNITION RESEARCH

Mr. Conte. Okay.

Welcome, Dr. Goldstein. I have enjoyed your testimony, and this year I am sure there will be no exception; I will enjoy it again.

We have worked closely together over the years on many special projects, and this past year we have seen the enactment of the Decade of the Brain. And I want to thank you for all you have done in making the Decade of the Brain come true.

I hear you are calling for more research in the areas of cognition within the brain. What might be learned by this research?

Dr. Goldstein. In the past, we have done the technically easier research, namely studies that were more readily available. We could measure what was going into the brain. We could measure what was coming out of the brain. They were measurable, so we could get at them, identify them and quantitate them.

But how does the brain really work, how do we think, how do we solve problems, how do we remember, do we ever forget anything? We have all had the experience of meeting somebody, we cannot remember his or her name; we walk away and 10 minutes later we recall what we thought we had forgotten.

We didn't forget it; the information was stored in our brain somewhere. It just wasn't able to pull it out. This entire area of research we label cognition. We are now beginning with the research tools we have, PET research. I am a little hesitant to say it, given that we are cutting the PET Centers. We can now go inside the brain and watch people think. If you remember my demonstration of that a few years ago.

We are now taking on the tough problem, how does the brain think, how does it learn, how does it remember? That is one of our new initiatives. It's one that is fairly low key at the moment, but we are moving ahead very steadily in that area.

HEAD INJURY

Mr. Conte. Last year and also here this morning, we heard a great deal about research needs in head injury. Thousands of Americans suffer head injuries every year.

What does your Institute consider the highest priority in head injury research, and what are you doing to implement the Interagency Head Injury Task Force Report?

Has the task force delivered its 1990 report as yet?

Dr. Goldstein. There were two reports, sir. The first, you remember, was delivered to the committee last year. The second is the most recent one the committee requested. It is my understanding that the second report was forwarded by the Department to this committee on Monday. I hope by now you have received it.

What you asked for recently were plans to implement two of the Task Force recommendations. One was for a national system of recording the incidence and the types of head injury. We have made a recommendation on that proposal.

The second was for the establishment of the National Advisory Board, which would oversee both research and patient services. We have also made a recommendation on that proposal. As I say, sir, I hope your staff received that report on Monday. It did leave the Department.

In regard to the section of the Task Force report, directly related to the recommendations of the Neurological Institute, that section was the research recommendations part of the report. With the very limited funds available to us this year, we were able to establish two new head injury research centers on a pilot study basis. One is in Boston and one is in Houston, Texas.

They have both been developed at a pilot level, in order for them and us to gain the experience necessary for a major effort. But that was all we were able to do to implement the Task Force recommendations on research.

NEUROFIBROMATOSIS

Mr. Conte. Your Institute is taking the lead in coordinating research on neurofibromatosis. What mechanisms do you have at your Institute and among other Institutes to coordinate the various research projects involved in a multi-system disease like NF?

Dr. Goldstein. There are two activities that serve to coordinate. The first is at the NIH itself. The NIH has a neurofibromatosis research clinic, which primarily involves both the Cancer Institute and our own Institute.

Also, at the NIH, there is a coordinated effort among the Institutes for neurofibromatosis research.

In terms of coordination in the non-government community, we lean heavily on the private sector neurofibromatosis associations to accomplish this, because they have the most intimate contact, with the patients afflicted. We support them in this effort, looking to the private sector for community coordination, rather than setting up another government activity.

ADVERTISING UNFUNDED PROJECTS

Mr. CONTE. Is there a possible mechanism at NIH that allows unfunded approved grants to be published and circulated for funding in the public sector?

Dr. GOLDSTEIN. No, sir. The Federal privacy law prohibits that. The law says that we are not permitted to acknowledge that we have a grant application, unless we fund it. It is against the law. I would go to jail if I did that.

NEUROFIBROMATOSIS

Mr. CONTE. We don't want that to happen. Please provide the committee a list of the specific research grants in NF that NINDS has exclusively funded in the past 3 years, along with their funding levels. Get that for the record.

[The information follows:]

NINDS GRANT AWARDS FY 87 THRU - FY 89

Project #	P.I./Location/Title	FY87 Dollars	FY88 Dollars	FY89 Dollars
P01 NS 24279	Breakefield, Xandra Eunice Kennedy Shriver Ctr Mtl Retardation Waltham, MA Molecular Genetics of Inherited Neurologic Diseases	458,369	442,591	439,278
R01 NS 16115	Maxwell, Gerald D. University of Connecticut Health Center Farmington, Connecticut Developmental Influences on Neural Crest Cells	128,176	106,820	102,869
R01 NS 20025	Martuza, Robert L. Massachusetts General Hospital Boston, Massachusetts Hormonal Modulation of Neurofibromatosis	263,779	251,941	0
R01 NS 21970	Pintar, John E. Columbia University New York, New York Molecular Studies of Growth Factors During Development	116,471	0	147,289
R01 NS 21997	Schmale, Michael C. University of Miami Coral Gables, FL A Model For Human Neurofibromatosis	57,874	0	0

NINDS GRANT AWARDS FY 87 THRU - FY 89

Project #	P.I./Location/Title	FY87 Dollars	FY88 Dollars	FY89 Dollars
R01 NS 22224	Gusela, James F. Massachusetts General Hospital Boston, Massachusetts DNA Marker Linkage Studies of the Phakomatoses	179,026	253,212	292,174
R01 NS 22936	Cavalli-Sforza, Luigi L. Stanford University Stanford, CA Linkage Analysis of Neurofibromatosis	138,251	134,169	0
R01 NS 23008	Pericak-Vance, Margaret A. Duke University Durham, NC Linkage in Huntington's Disease and Neurofibromatosis	208,374	186,800	0
R01 NS 23476	Anderson, David J. California Institute of Technology Pasadena, California Molecular Biology of Neural Crest Development	149,817	149,760	208,769
R01 NS 23883	Ciment, Gary S. Oregon Health Sciences University Portland, Oregon Neurofibromatosis-A Model System Using Phorbol Esters	94,010	91,403	122,157

NINDS GRANT AWARDS FY 87 THRU - FY 89

Project #	P.I./Location/Title	FY87 Dollars	FY88 Dollars	FY89 Dollars
F32 NS 07754	Aletta, John M. New York University New York, New York The Role of Phosphoproteins in NDF's Mechanism of Action	24,996	0	0
F32 NS 08232	Bitler, Catherine M. Stanford University Stanford, California Mechanism of Action of Nerve Growth Factors	18,996	0	21,000
F32 NS 07967	Burcham, Timothy S. Stanford University Stanford, California Nerve Growth Factor Receptors	24,996	0	0
K07 NS 00856	Mehler, Mark F. Yeshiva University Stanford, California The Molecular Pathology of Acid Maltase Deficiency (AMD)	60,048	59,255	58,752
K08 NS 01015	Mobley, William C. UC - San Francisco San Francisco, CA Nerve Growth Factor-Effects on Developing CNS Neurons	76,896	0	0

NINDS GRANT AWARDS FY 87 THRU - FY 89

Project #	P.I./Location/Title	FY87 Dollars	FY88 Dollars	FY89 Dollars
K08 NS 01018	Milbrandt, Jeffrey D. Washington University St. Louis, Missouri Developmental Expression of Genes Regulated by NGF	70,041	69,947	57,536
R01 NS 04270	Shooter, Eric M. Stanford University Stanford, California Nerve Growth Factor in Neuronal Development	354,825	345,908	359,099
R01 NS 10259	Black, Ira B. Cornell University Medical Center New York, New York Regulation of Neuronal Growth and Development	154,251	143,498	148,053
R01 NS 18071	Johnson, Eugene M. Washington University St. Louis, Missouri Central Process and NGF in the Life of Sensory Neurons	0	159,332	165,524
R01 NS 18218	Halegoua, Simon SUNY Stony Brook Stony Brook, New York Molecular Mechanisms of Neuronal Differentiation	127,516	120,711	159,127

NINDS GRANT AWARDS FY 87 THRU - FY 89

Project #	P.I./Location/Title	FY87 Dollars	FY88 Dollars	FY89 Dollars
R01 NS 18616	Lee, Virginia M. University of Pennsylvania Philadelphia, PA Regulation of Neurofilament Phosphorylation & Expression	195,160	220,244	214,993
R01 NS 18708	Perez-Polo, Jose R University of Texas Med Br Galveston Galveston, Texas Characterization of Neuronotrophic Factors	144,042	160,439	170,205
R01 NS 19964	Bradshaw, Ralph A UC Irvine Irvine, California Structure and Function of Nerve Growth Factor	197,227	195,924	202,153
R01 NS 20013	Kessler, John A. Yeshiva University New York, New York Mechanism Governing Neuronal Development	131,563	0	188,494
R01 NS 21072	Chao, Moses Victor Cornell University Medical Center New York, New York Molecular Biology of the Nerve Growth Factor Receptor	146,453	145,879	148,871

NINDS GRANT AWARDS FY 87 THRU - FY 89

Project #	P.I./Location/Title	FY87 Dollars	FY88 Dollars	FY89 Dollars
R01 NS 21716	Ross, Alonzo H. Worcester Foundation for Experimental Biology Shrewsbury, MA Characterization of Nerve Growth Factor Receptor	163,660	214,023	206,132
R01 NS 21824	Reichardt, Louis F. University of California San Francisco San Francisco, CA NGF Synthesis in Sites Relevant for the Nervous System	79,878	0	0
R01 NS 22470	Rosenau, Werner University of California San Francisco San Francisco, CA Pathology: Onogenes in Differentiation and Neoplasia	79,572	0	0
R01 NS 22475	Messing, Albee University of Wisconsin Madison Madison, Wisconsin Neuropathology Due to Oncogene from SV40 Virus	63,640	0	88,327
R01 NS 23075	Fahnstock, Margaret SRI International Menlo Park, California Nerve Growth Factor Genes	103,190	96,975	0

NINDS GRANT AWARDS FY 87 THRU - FY 89

Project #	P.I./Location/Title	FY87 Dollars	FY88 Dollars	FY89 Dollars
R01 NS 23343	Bothwell, Mark A. University of Washington Seattle, Washington Nerve Growth Factor	158,116	145,975	153,599
R01 NS 24251	Stach, Robert W. Health Science Center at Syracuse Syracuse, New York Type I Nerve Growth Factor Receptor Reactive Serine	95,308	91,976	94,179
R01 NS 24321	Rutkowski, Julia L. Johns Hopkins University Baltimore, Maryland Nerve Growth Factor Synthesis by Cultured Schwann Cells	56,445	53,392	58,005
R01 NS 24380	Neet, Kenneth E. Case Western Reserve University Cleveland, Ohio Structure and Function of Nerve Growth Factor	109,018	100,098	190,212
R01 NS 24387	Feinstein, Stuart C. University of California Santa Barbara Santa Barbara, California NGF, Neurite Outgrowth and Microtubule Assembly	102,087	78,790	69,752

NINDS GRANT AWARDS FY 87 THRU - FY 89

Project #	P.I./Location/Title	FY87 Dollars	FY88 Dollars	FY89 Dollars
R01 NS 24679	Johnson, Eugene M. Washington University St. Louis, Missouri NGF Receptors on Schwann Cells	193,037	171,981	0
R29 NS 24747	Isackson, Paul J. University of California Irvine Irvine, California Structure of Biologically Active Nerve Growth Factor	86,187	79,981	80,884
R01 NS 25169	Loy, Rebekah University of Rochester Rochester, New York Development of Nerve Growth Factor Sensitivity	149,595	129,930	131,361
	TOTAL	4,960,890	4,400,954	4,278,794

MAGNETOENCEPHALOGRAPHY

Mr. Conte. Please provide a list of the NF research grants that NINDS has done in corroboration with other Institutes in the past 3 years within the funding levels.

[The information follows:]

National Cancer Institute

Neurofibromatosis Awards FY 1987 - FY 1989

Project #	P.I./Location/Title	FY87 Dollars	FY88 Dollars	FY89 Dollars
R01 CA 11751	Little, John B. Harvard University Boston, Massachusetts Effects of Radiation on Stationary Cells	$69,627	0	0
R01 CA 28110	Young, David M. University of Florida Gainesville, Florida Nerve Growth Factor and Granulopoiesis	4,817	$4,702	0
R01 CA 28854	Skolnick, Mark H. University of Utah Salt Lake City, Utah Genetic Epidemiology of Cancer in Utah Genealogies	50,333	56,588	$22,555
R01 CA 29275	Meadows, Anna T. Children's Hospital of Philadelphia Philadelphia, Pa. The Epidemiology of Childhood Brain Tumors	18,743	20,273	17,186
R01 CA 31777	Davidson, Richard L. University of Illoinis at Chicago Chicago, Illoinis BUDR Dependence, Malignancy, and Differentiation	32,910	33,363	34,133
R01 CA 36362	Bishop, David T. University of Utah Salt Lake City, Utah Linkage Analysis and Multiple Loci	0	31,593	32,199

National Cancer Institute

Neurofibromatosis Awards FY 1987 - FY 1989

Project #	P.I./Location/Title	FY87 Dollars	FY88 Dollars	FY89 Dollars
R01 CA 38685	Rowley, Peter T. University of Rochester Rochester, New York Detecting Inherited Cancer Predisposition Via Oncogenes	102,889	104,926	0
R01 CA 41527	Bothwell, Mark A. University of Washington Seattle, Washington Nerve Growth Factor & the Physiology of Neural Crest	9,705	9,499	0
R37 CA 43175	Shore, Roy E. New York University New York, New York Follow-up of Patients X-Irradiated for Scalp Ringworm	19,029	18,173	13,400
R01 CA 47082	Preston-Martin, Susan University of Southern California Los Angeles, California Childhood Brain Tumors and N-Nitroso Exposures	0	17,842	16,169
	TOTAL	308,053	296,926	135,642

MAGNETOENCEPHALOGRAPHY

Mr. CONTE. Dr. Goldstein, your Institute has taken the lead in biomagnetic imaging. The body's electrical activity could be analyzed by this new technology. What efforts are under way at your Institute to investigate future applications of this technology?

Dr. GOLDSTEIN. Two separate efforts, sir. The first one is that which we have within our own laboratory, at the Neurological Institute Laboratory at Bethesda. It is one of the national focal points for magnetoencephalography research.

Second, we have made research grants for this purpose to four separate organizations, one in Massachusetts, one in New Mexico and two in California. Magnetoencephalography not only requires brain scientists, but also requires physicists who understand magnetism. There are relatively few places available at this time with that combination of research skills.

Interestingly enough, a chance observation by a former employee of the Ford Motor Company made the first direct recording of the magnetoencephalogram possible.

Mr. CONTE. I will be darned.

Dr. GOLDSTEIN. At the time he had probably the most advanced technology in this research area in the world.

MUSCULAR DYSTROPHY

Mr. CONTE. I hear there is promise in new studies involving shots of healthy muscle cells for muscular dystrophy. What is the current status of this research, and is it a promising new treatment?

Dr. GOLDSTEIN. Oh, yes. What we are discussing is the implantation of young muscle cells into the patient who has muscular dystrophy. Will that muscle cell produce the missing enzyme called dystropin? The answer to that is yes.

Second, will that implant stay alive long enough for the patient to have any benefit? The answer in animals is yes. The answer in patients is we don't yet know.

And so, the implantation of very young muscle cells from a normal person into a person with muscular dystrophy is on the horizon; it works in animals, perhaps next year I will be able to tell you whether it works in humans.

MULTIPLE SCLEROSIS

Mr. CONTE. I hope so.

I understand your Institute is involved in a new strategy for treating multiple sclerosis. It involves shutting down just part of the immune system. You have done studies in mice, and can you tell us where the project is now, and what is known about the possibility of viral causes of MS?

Dr. GOLDSTEIN. The project has gone through our review system, it is a multi-million-dollar project for a controlled clinical trial. It has been through the review system; it has been approved, and I am sorry to say, I don't yet know if we will be able to fund it.

Mr. CONTE. I am sorry to hear that. How much would it cost?

Dr. GOLDSTEIN. $1,625,000 a year for each of 4 years.

PCR TECHNIQUE

Mr. CONTE. PCR technique is making big contributions to biomedical research. I think the best potential of this technique has yet to come. Are your scientists using PCR?

Dr. GOLDSTEIN. Oh, yes, sir. It was the hard-core technological basis of the muscular dystrophy genetic breakthrough, the finding of the muscular dystrophy gene. It is also being used very actively in the search for better tests for AIDS. I am sure Dr. Fauci will be able to discuss that in much more detail than I can.

SEQUESTRATION

Mr. CONTE. What are the effects of sequestration and other budgetary reductions on your Institute programs, and what research efforts have been endangered by sequestration?

Dr. GOLDSTEIN. Our Institute lost something in the order of magnitude of $5,500,000 due to sequestration. Those funds had to be taken from both the PET centers and the Javits Center of Excellence program.

So, rather than only spread it around, if I can use that term, we targeted the cuts into two programs and had those two bear the burden.

Mr. CONTE. I guess my time is up, Mr. Chairman.

Mr. NATCHER. Mr. Stokes, I yield to you.

STROKE

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Goldstein, it is always a pleasure to welcome you before the subcommittee. In your opening remarks, you stated that incidence of stroke is now rising, but that you do not know why.

You also stated, even low birth weight infants suffer mortality and morbidity resulting from brain hemorrhage.

Dr. GOLDSTEIN. Yes, sir.

Mr. STOKES. Can you quantify this increase in incidences for us?

Dr. GOLDSTEIN. I should be able to—I am very sorry, Mr. Stokes, I am just blanking out. As I explained, maybe in 3 or 4 minutes, it will come back to me.

[CLERK'S NOTE.—Response provided in record questions.]

But there has been a surprising—not just a little bit, a surprising increase in the occurrence of new cases of stroke reported in two separate studies. The problem with both of those studies, if I might elaborate, is they are in white populations. They were the only long-term groups under study and so we have a paucity of data about stroke incidence in non-white populations.

We have now established one study in Harlem to see if that is true in a black population, and we are exploring the development of a human population laboratory for blacks possibly in the City of Baltimore. For example, can the entire Civil Service of the City of Baltimore, which ranges from men who dig the ditches to the Mayor of the City be studied? Can we follow them over time to learn the answer to the question of what occurs in blacks, because we would then have a stable population of people that we can test regularly over time.

In discussion with the University of Maryland, we are exploring plans for a black study of stroke there.

Mr. STOKES. Last year, you will recall that you and I had an interesting exchange about a program announcement that NINDS had issued to encourage the submission of research grant applications in the area of stroke in black populations. You told me at that time that you had only gotten two applications in response, and that you were only able to fund one of them.

I understand that you have again sought applications in this area. Can you tell us what the result was?

Dr. GOLDSTEIN. We received four applications, sir. They are presently in the review process. It is for that reason that we decided to move ahead aggressively and go to our colleagues in Baltimore and in Harlem and say, let us work with you to develop a proposal, rather than take the passive grant route, saying wouldn't you please apply?

And so, we are now moving ahead more aggressively.

Mr. STOKES. Now, last year, you also told me that there is more than one type of stroke, and that one type is more common in blacks than in whites. I would like for you to review that for me, and also tell me the status of studies the Institute is conducting which compare stroke in African populations with stroke in the African-American population.

Dr. GOLDSTEIN. To your first question, sir, there are two—in very general terms, there are two kinds of blood vessels feeding the brain. One type is fairly large and distributes over the surface of the brain, and underneath the base of the brain.

In whites, those larger blood vessels get clogged up with atherosclerosis, primarily. In blacks and in Asians, Asians who are not in the United States but rather Asians in China and in Japan, the small blood vessels that leave the large ones penetrate into the depths of the brain. These very small blood vessels are the ones that cause strokes in blacks and in the Asians I have described.

Now, I have got to be careful. Blacks in our country unfortunately are under double jeopardy. They get small vessel disease plus the disease of the larger blood vessels at the base of the brain. That is one of the reasons, not the only reason, why the incidence of stroke and stroke mortality has been so high in blacks. Blacks get it from each cause, while whites have pathology predominately in the big blood vessels at the base and on the surface of the brain.

Your second question——

Mr. STOKES. About the African studies you have, comparing them to African-American studies.

Dr. GOLDSTEIN. We have done a comparative study using a stable black population in Copiah County, Mississippi, and compared that group with the patient population in Nigeria, under the leadership of Professor Osuntunkun. I must say, sir, I have gone there personally and examined patients, and we find that the type of stroke in both populations is very similar.

They are the same. Now, please don't ask me what that means. I was looking for a difference, because a difference we thought would give us leads to etiology. The fact that we didn't get a difference shook us up, but there is the same kind of disease in both populations.

Mr. STOKES. Now, in this area of your budget, how much are you requesting for stroke research related to the differential between white and black Americans?

Dr. GOLDSTEIN. Yes, sir. Our stroke budget in this fiscal year is approximately $46,000,000. Approximately 20 percent of that relates to studies of incidence and mortality in blacks.

Mr. STOKES. How about your program you just told us about in Baltimore? How much is that program?

Dr. GOLDSTEIN. It will require about $1,500,000 a year.

Mr. STOKES. How much?

Dr. GOLDSTEIN. Such a study would require about $1,500,000 a year.

Mr. STOKES. Over what period of time will you do it?

Dr. GOLDSTEIN. Five years, sir.

SLEEP RESEARCH/NARCOLEPSY

Mr. STOKES. What progress has been made in the area of sleep research, Doctor? I understand you have some insights in the anatomy of narcolepsy.

Dr. GOLDSTEIN. Let me address that in two parts, because you have asked two questions. We spend a lot of our 24 hour day asleep; I hope we do, anyway. And you know, we don't understand what is going on in the brain when we are asleep. It is not a resting brain, it is not a brain that has been turned off. It is very active and doing all kinds of things, but how it does it, is what we don't understand. What is going on physiologically and chemically? What areas are active? What areas are passive?

And so, we are practically at base line trying to understand, what is sleep? What parts of the brain are doing what, and what is controlling the brain status we call sleep? One disease or disorder of sleep is called narcolepsy. If I had narcolepsy, while talking to you I could suddenly collapse and literally be asleep; I would wake up, look refreshed, talk with you again and then, suddenly fall off to sleep again.

Fortunately, we do have an animal model of this disorder. The animal model is at Stanford University, where these animals, purebred dogs, develop narcolepsy. They walk along and suddenly, they fall on the floor, fast asleep.

And so, we are trying in that animal model to understand not only what is going on, but also evaluating a number of drugs that may be useful in therapy.

The last comment I should make is the Sleep Commission has now been organized by the Secretary. The Congress asked that there be a Sleep Commission, a group of world experts to evaluate sleep research. The Commission will be meeting in 3 weeks to discuss the directions of sleep research for the future.

NEUROLOGICAL IMPLICATIONS OF CRACK

Mr. STOKES. Doctor, I am concerned about the use of crack in our society, and all the ramifications of that. I am wondering if we are doing any long-range neurological studies related to the usage of crack?

Dr. GOLDSTEIN. Not enough. We now know that between the age of 12 and 20, crack is causing stroke. That is a fact. The mechanism may be inflammation of the arteries. How do we intervene? What do we do for these young people either to diminish the occurance of stroke or treat it? There is no organized effort to answer these questions.

The second issue I am sorry to report, is our PET Centers were just beginning to look at what goes on in the brain of a crack drug abuser, not how does the patient react, but what is going on inside that brain that makes the crack user want more crack? What do we mean by addiction from a brain metabolic and neurological perspective.

Our PET Centers were beginning to study these questions. Because of the need to assign available funds for the support of individual research grants, we have had to eliminate those projects and suggest that PET Centers turn to the drug abuse agency for support.

CHILDREN WITH NEUROLOGICAL AIDS

Mr. STOKES. My last question—are you studying the long-term neurological complications of children with AIDS or HIV infection?

Dr. GOLDSTEIN. Let me start with the short term. These children who have AIDS, often infants, are very severely damaged. Most of their developmental milestones have been destroyed. And so we are focusing on those immediate brain effects of AIDS, rather than the long term effects. For the most part, the damage is very acute and usually threatens their survival. These studies are collaborative with NINDS, NICHD and NIAID.

What we do know is that the drug AZT seems to ameliorate the developmental deficits, particularly in the brain. If you don't mind, sir, I would hope that you address your question for more detail to Dr. Fauci, who is a world authority on that subject. I am kind of on thin ice and I don't want to get in much deeper.

Mr. STOKES. We will reserve and ask him some questions on that.

Mr. NATCHER. Mr. Early, I yield to you.

LASER TREATMENT OF STROKE

Mr. EARLY. Thank you, Mr. Chairman.

Doctor, how much research is the Institute doing with regards to treating stroke with lasers?

Dr. GOLDSTEIN. There is one form of stroke in which it is thought that lasers may be useful. It is the kind of stroke in which a lot of very small blood vessels resemble a jungle between the artery going in and the vein going out. It is called an arterial-venous malformation. Lasers may be useful in cauterizing the area to destroy the small blood vessels.

We now have a technique, a surgical technique in which using a computer, a CAT scan, and steriotaxis, which is putting a helmet on the head to isolate a very small area, a laser beam, and actually what is even better is a gamma beam can be directed to a pin point in the brain to cauterize that area.

If we try to do that without the beam, we would destroy a large portion of the brain. The laser technique has also been suggested to clean out the inside of an obstructed artery to the brain.

Mr. EARLY. So, Doctor, are you doing a lot of work with lasers or not?

Dr. GOLDSTEIN. Not a lot.

Mr. EARLY. I talked to a group that is really enthusiastic about this, suggesting that laser use in stroke will be—I mean, cleaning of the arteries and all that, will be done by laser.

Dr. GOLDSTEIN. I don't know about that surgical intervention.

DOWNWARD NEGOTIATIONS

Mr. EARLY. These were professional people. Doctor, what is your downward negotiation on competing research projects in 1991?

Dr. GOLDSTEIN. I am sorry, sir. Would you say that again?

Mr. EARLY. What is your downward negotiation for competing research grants for 1991? For competing research grants, what is the adjustment for downward negotiation?

Dr. GOLDSTEIN. What we are doing——

Mr. EARLY. Percentage-wise, Doctor, I want a percentage.

Dr. GOLDSTEIN. It is an average of 12 percent.

Mr. EARLY. Doctor, that is not—I have numbers that the last several Directors have all confirmed. My numbers show, for NINDS, that the downward negotiation for 1991 for competing research grants is 25.1 percent.

Dr. GOLDSTEIN. Our proposed plan is 12 percent rather than the 25 percent shown on the tables.

Mr. EARLY. Dr. Raub, will you——

Mr. NATCHER. Mr. Early, would you yield to me at this point?

Dr. Raub, I asked the same question, as you know, of our friend, Dr. Goldstein. Now, Dr. Raub, as you know, the committee uses the NIH history tables, which you submit, as a key element in its review of your budget. We use them for all the Institutes.

Dr. Goldstein has indicated that these tables are in error as far as his Institute is concerned. Just briefly now clarify this for the committee, and Mr. Early, thank you, because we have to use those tables. What about this, Dr. Raub?

Dr. RAUB. Insofar as the one particular number is concerned, we will have to clarify that for the record. But we take very seriously the compilation of the data that come to you, because we know you rely upon it heavily. I have the minus-25 percent number on my tables as well. It was not invented in the central office. There was some confusion in terms of the hand-off of numbers from Dr. Goldstein's Institute to the Office of the Director.

We will clarify that one particular number, but to the best of my knowledge, the rest of this table is accurate.

[The information follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

National Institute of Neurological
Disorders and Stroke
Bethesda, Maryland 20892
Building: 31
Room : 8A52
(301) 496-9746

March 30, 1990

To: Chairman, House Subcommittee on Labor, Health and Human Services, Education
THROUGH: Acting Director, NIH W F Raub 30MAR90

From: Director, NINDS

Subject: Cuts in NINDS Competing Grant Awards for Fiscal Year 1991

Please allow me to elaborate on my recent testimony before the House Appropriations Subcommittee regarding the President's Budget for the National Institute of Neurological Disorders and Stroke for Fiscal Year 1991.

The NIH tables as presented to the Subcommittee accurately capture the original data that the NINDS provided to the Office of the Director, NIH, consistent with the guidelines established by that office. They correctly indicate that the NINDS would have to downward negotiate nearly all competing research project grants by 25 percent in order to award 405 competing grants within the resources the NIH has identified for research project grants in the FY 1991 President's Budget.

As I reviewed our allocation of FY 1991 resources for research project grants, I became concerned that downward negotiations of 25 percent from projected full study section recommended levels would prevent an investigator from fully meeting the objectives of an approved research project. I therefore intend to adjust the FY 1991 request for NINDS in order to reduce the downward negotiation rate on new and competing grants to 12 percent. This revision would result in a reduction in the number of new and competing grants supported in 1991 by 51, from 405 to 354. I believe it would be better to reduce the number of competing research project grants in 1991 in order to maintain the downward negotiation rate for each project at 12 percent.

In addition, NINDS also intends to reduce the number of new and competing grants in 1990 by 56, from 471 originally estimated to 415. The 1990 revision would limit downward negotiations to 12 percent in 1990 for new and competing grants. With the revised downward negotiations, the funded average cost for new and competing grants will increase from $170 thousand in 1989 to $203 thousand in 1990. The average cost for 1991 will be approximately $200 thousand.

My comments made during the hearing regarding the NINDS downward negotiation rates were made with these budget revisions in mind. Again, the NIH tables indicating a 25 percent downward negotiation rate are correct in that awarding 405 competing grants would require reductions of this magnitude. However, as stated above, the NINDS now proposes to fund 354 competing research grants at a downward negotiation rate of 12 percent. Appropriate revisions to the FY 1991 Congressional Justification provided earlier to the Subcommittee will follow shortly.

I regret if my oral remarks resulted in confusion regarding the President's Budget.

Murray Goldstein, D.O., M.P.H.

Mr. EARLY. To what pay line percentile will you fund under your 1991 request, Dr. Goldstein, and how does this compare to the two past fiscal years?

Dr. GOLDSTEIN. Last year and this year, we funded through the 12th percentile. We will now fund through the 10th percentile.

Mr. EARLY. Does that concern you? Does that disturb you, Doctor?

Dr. GOLDSTEIN. Yes, sir.

Mr. EARLY. So, for one of the most noted researchers, if his grant fell in the 16th percentile, he will not be funded?

Dr. GOLDSTEIN. Unless there is something extraordinary about that grant, he will not be funded.

Mr. EARLY. That is worse than we have ever done, isn't it, Doctor?

Dr. GOLDSTEIN. That is correct, sir.

Mr. EARLY. Doctor, what effect is this having on the research projects supported with these grants, and what effect will another year of steep downward negotiations have?

Dr. GOLDSTEIN. It will cut their productivity in a large way.

Mr. EARLY. What is curious, Doctor, as far as—you would think one would offset the other, but it appears that the number of grants is declining, and the downward negotiation is increasing; is that accurate?

Dr. GOLDSTEIN. Yes, sir.

Mr. EARLY. How? Why?

Dr. GOLDSTEIN. Each grant now, the grant average cost has risen. It is going up in the Neurology Institute by about 5 percent a year for each of the last 2 years.

Mr. EARLY. At the end of the year, with your downward negotiation, will it be still higher or less than it was the previous year?

Dr. GOLDSTEIN. With higher negotiations.

Mr. EARLY. On the one hand, you tell us the grant that we are going to fund—and this is what is happening, you are telling us that the grant is increasing, but after downward negotiation, it might be less than they had the previous year; is that it?

Dr. GOLDSTEIN. No. What we are doing is this: we are telling an investigator, you will not get more than you got last year, plus 4 percent, irrespective of what your approved budget is. We are holding the grant award at last year's level, plus 4 percent.

Mr. EARLY. It doesn't matter if it is the most exciting science you have ever seen in the Institute's history.

Dr. GOLDSTEIN. If you remember, I said, with the exception of extraordinary circumstances.

Mr. EARLY. Can you provide for the record how many extraordinary circumstances you identified in 1990, and how many——

Dr. GOLDSTEIN. In fiscal year 1990, 23 research grants were awarded at the level recommended without administrative cuts.

RESEARCH CENTERS

Mr. EARLY. Doctor, you plan to fund about 29 research centers in 1991, the same as in 1990, yet it is the same amount of funds?

Dr. GOLDSTEIN. Yes, sir.

Mr. EARLY. How are we doing that?

Dr. GOLDSTEIN. By cutting the budget of each one.

HUNTINGTON'S DISEASE

Mr. **Early**. Doctor, each year, you tell us—you tell the committee that the advances that have been made in the area of Huntington's disease have been very impressive. Will we ever get a cure for Huntington's disease, in your professional opinion?

Dr. **Goldstein**. I think we will have a treatment for Huntington's disease within my professional lifetime.

Mr. **Early**. Do you think we will ever have a prevention for Huntington's?

Dr. **Goldstein**. I think we will have a treatment but I don't know whether a prevention will be available in my professional lifetime.

Mr. **Early**. Why, Doctor? I mean, we have identified a gene. What good does it do to identify all these things if we are not going to cure them or better treat them?

Dr. **Goldstein**. Well, that was one of the reasons I discussed the strategy for the treatment of Gauchers Disease, a treatment which we have never been able to do before. There are at least three issues. The first is to define that elusive gene that keeps slipping away from us. As a matter of fact, it may be in the other direction than we previously thought. We have had to split our effort into two teams, one working in each direction on the chromosome.

The second is once we find the gene, we have got to find out what it does produce that is abnormal or doesn't produce that is necessary. My guess is that it is producing something that is injurious, but we don't know that yet. We are going to have to discover the nature of that material, but for the moment, let me call it an enzyme.

The third is, after we have identified the enzyme, will we be able to give it to the patient so that the patient can use it? And that is what I meant by our Gauchers studies developing a template that for the first time permits us to give a replacement enzyme effectively.

It worked for Gauchers, will it work for Huntington's, I don't know.

Mr. **Early**. I thought a couple of years ago, Doctor, in one of your charts, you showed us an oncogene that was going to show us that. Aren't the oncogenes the fighting genes that are supposed to correct these things?

Dr. **Goldstein**. That was not my testimony.

GAUCHERS DISEASE

Mr. **Early**. Okay, fine. Doctor, on the Gaucher, those are very illustrative examples for a lay person. You showed a boy that had problems and then you showed a boy that appeared to be all right, and you said that you hadn't cured it, maybe you just treated it.

But the treatment—I mean, is that boy going to grow up and lead a normal life?

Dr. **Goldstein**. I hope so. The reason I say it that way is if you recall, I said we don't know what the long-term effects will be. This child has been treated for 6 months. Will the enzyme replacement therapy work in 6 years? Nobody has ever been there. We don't know.

Mr. **Early**. You don't know it isn't going to be there?

Dr. **Goldstein**. Absolutely.

Mr. **Early**. You may recall that Mr. Livingston, was interested in Gaucher's, and it looks like you have made a lot of progress.

Dr. **Goldstein**. We have made progress. There is hope now, realistic hope.

Mr. **Early**. I will supply the rest of my questions for the record. Thank you, Mr. Chairman.

Mr. **Natcher**. Yes.

Dr. Goldstein, we want to thank you and your associates for appearing before our committee at this time on behalf of your budget request for the fiscal year 1991. It has been a good hearing, Doctor. As I said to you a few months ago, with your help and Dr. Raub's help and others, we are going to produce a good bill.

Dr. **Goldstein**. Thank you very much, sir.

Mr. **Natcher**. Thank you, sir.

Mr. **Conte**. Doctor, I want to join with the chairman. I think as usual, you did an excellent job. I am sorry, I have got about another 30 questions to ask you. You look them over, you answer them as if I have asked you.

Dr. **Goldstein**. I will do just that.

Mr. **Conte**. It is too bad. They are really good questions. You will look forward to it.

[Questions and answers for the record and the justifications follow:]

DISEASE EXPENDITURE ESTIMATE 1989-1991

Mr. Natcher. Provide an estimate of your Institute's spending on the following diseases or conditions for 1989-1991: Huntington's Disease, multiple sclerosis, neurofibromatosis, muscular dystrophy, stroke, epilepsy, head injury, and spinal cord injury.

Dr. Goldstein. The following table lists NINDS actual and estimated spending for FY 1989 through FY 1991 for the diseases requested.

Disease/Disorder	1989 Actual	1990 Estimate	1991 Estimate
Epilepsy	$38,327,000	$39,550,000	$41,371,000
Head Injury	21,157,000	21,832,000	22,837,000
Huntington's Disease	29,612,000	30,557,000	31,154,000
Multiple Sclerosis	46,255,000	47,731,000	49,927,000
Muscular Dystrophy	3,706,000	3,824,000	4,008,000
Neurofibromatosis	4,497,000	4,641,000	4,855,000
Spinal Cord Injury	36,036,000	37,186,000	38,898,000
Stroke	44,928,000	46,362,000	48,496,000

NERVE PACEMAKERS

Mr. Conte. What are some of the potential clinical uses of nerve pacemakers?

Dr. Goldstein. Neural prostheses or "nerve pacemakers" are devices which make direct electrical connections with the nervous system to restore or supplement neurological function. They are already being used successfully to provide hand grasp for individuals with paralyzed upper extremities, to permit spinal cord injury victims to voluntarily evacuate their bladders and to restore limited hearing to the totally deaf. Potential future applications include restoration of sexual functions in people with spinal cord disorders and ambulation for paraplegic individuals.

Mr. Conte. What is the status of your work in this field?

Dr. Goldstein. A system to provide hand grasp to paralyzed individuals is now being evaluated at multiple rehabilitation centers. Artificial sensory transducers are being developed to restore the sense of touch in these individuals. Long term acceptance will be increased with the incorporation of more reliable electrodes which are now in the design stage.

An early version of the bladder evacuation system based on electrical stimulation of the nerves as they leave the spinal cord is now commercially available. A more sophisticated system that includes control of sexual functions utilizes microstimulation of the sacral spinal cord and is now in the research feasibility stage.

Cochlear implants for the deaf were developed over the past 20 years by investigators supported by NINDS and are now implanted in over 3000 deaf users. All projects on the development of improved auditory prostheses are now administered by the new National Institute on Deafness and Other Communication Disorders, but scientific leadership is provided by scientists in the NINDS Neural Prosthesis Program.

PARKINSON'S DISEASE

Mr. Conte. I am happy to hear that your Institute was instrumental in the development and testing of Deprenyl, the drug found to slow the effects of Parkinson' s disease. What's next? Is there anything new in our knowledge on how Parkinson's gets started or how it progresses?

Dr. Goldstein. The findings obtained in the multi-center clinical trial of deprenyl are so striking that the trial was modified to provide deprenyl to all patients in the continuing study. Although the investigators are still unsure exactly how deprenyl works, they believe that this is the first drug which may slow the progress of a neurodegenerative disorder.

The dramatic results obtained in Parkinson disease patients have encouraged continuation of the trial to determine the effect of long term deprenyl treatment in association with L-DOPA therapy, and the possible additional benefit of the anti-oxidant, Vitamin E.

Initial results from studies with MPTP-treated monkeys (an animal model for Parkinson's disease) suggest that abnormal timing and directional activity of movement-preparatory cells in the brain leads to disorganized nerve firing patterns. Results from in vitro experiments consistently indicate that MPTP operates by inhibiting the energy producing cellular structures, called mitochondria, within nerve terminals of dopamine-producing cells.

In a new line of research, an NINDS grantee is investigating the functioning of mitochondria in Parkinson's disease patients. This investigator reported a 50 percent reduction of an important mitochondrial enzyme in the patients studied. Theoretical considerations suggest that mitochondrial abnormalities may also play a part in a number of other neurological disorders.

NERVE REGENERATION AND GROWTH

Mr. Conte. Research on nerve regeneration has important implications for a wide spectrum of degenerative diseases and neuronal injury. Can you tell us what your institute is doing in looking at this promising area?

Dr. Goldstein. NINDS serves as the national focal point for research on neural regeneration. Recent research on injury and regeneration in the central nervous system has led to a spirit of new optimism that injured neurons can survive and that regrowth of injured axons is possible. NINDS grantees and scientists are pursuing several avenues of research in this area. NINDS grantees are studying the use of synthetic guidance channels to provide a template for severed nerves to regenerate. This work may provide a new type of prosthetic device to enhance nerve growth. Other investigators are studying nerve growth factors and their role in promoting nerve repair and regeneration. Studies of the implantation of tissues and cells also suggests that these techniques may promote nerve fiber growth, particularly after spinal cord injury.

AIDS AND NEUROLOGY

Mr. Conte. What progress has been made in delaying the neurological complications of AIDS?

Dr. Goldstein. Recent evidence from the therapeutic trials with anti-retroviral agents strongly suggests that the progressive encephalopathy in children with HIV infection can be arrested or reversed. In some cases, brain imaging studies demonstrate resolution of atrophic changes normally associated with AIDS infection. In adults, progression of AIDS dementia complex can be halted and sometimes reversed. A joint NINDS-U.S. Navy project has been initiated which is focusing on the issue of how the brain is affected by AIDS.

Mr. Conte. What are some of the medications that hold particular promise in slowing the AIDS virus in the nervous system?

Dr. Goldstein. At present, AZT and DDI (dideoxyinosine) are the most effective drugs in controlling HIV infection. AZT delays progression of AIDS and, given early, prevents or delays development of neuro-AIDS. Although AZT crosses the blood brain barrier, therapeutic concentration of the drug in the central nervous system is lower than in peripheral blood, and the drug is eliminated from the central nervous system rapidly. Consequently, there is a desperate need to develop new drugs to treat neuro-AIDS. Research supported and conducted by the Institute to understand the development of HIV infection in the nervous system will provide insights for the development of better medications to delay or prevent the neurological complications of AIDS.

From these studies we know that HIV infection in the brain has different manifestations in children and adults. In adults infected with HIV, PET studies show a global reduction in metabolism, especially in subcortical structures. Peripheral neuropathies are common. Conversely, children with AIDS show evidence of cortical changes--microcephaly in the younger children and cortical atrophy in the older children.

GRANT CEILING IMPACT

Mr. Conte. Dr. Goldstein, We've heard that NINDS has imposed a ceiling of $750,000 on program project and center grants. What has been the impact on research programs -- in the PET centers, for example?

Dr. Goldstein. We just began to phase in the $750,000 ceiling for new and competing program project and center grant applications. The new ceiling will mean a reduction in funds for current PET centers by 30-50 percent. This reduction will translate into fewer studies. Plans to expand the use of PET to studies of various neurotransmitters, and the study of patients with Alzheimer's disease, drug and alcohol addiction, Parkinson's disease and movement disorders are on hold. As other investigators come in with competing PET center applications subject to the $750,000 cap, they will need to eliminate projects or curtail the scope of work to remain under the cap.

DYSTONIA

Mr. Conte. What has been the Institute been doing in improving research in dystonia?

Dr. Goldstein. The NINDS supports research to find the defective gene(s) responsible for the inherited forms of dystonia. Progress has been made in that a genetic marker has been found in a region of chromosome 9. Identification of a dystonia gene will create numerous research opportunities to identify and characterize the gene product and develop targeted methods to prevent and treat the disease. In other studies, intramural investigators have achieved encouraging results with the use of botulinum toxin to treat some types of dystonia.

CLINICAL TRIAL STATUS

Mr. Conte. What kinds of research advances are ready for evaluation by clinical trials?

Dr. Goldstein. We are in an exciting time in neuroscience research in which years of laboratory investigations and clinical observations have provided insights into possible treatments and preventive strategies for many neurological and neuromuscular diseases. For instance, knowledge of immune system involvement in multiple sclerosis suggests several approaches to treat this disease. Elucidation of the cellular and metabolic dynamics that result in nerve cell damage and death, both from trauma and degenerative diseases, has spurred efforts to find and evaluate pharmocologic agents to intervene clinically in these processes. With better understanding of nerve cell physiology, we are working to develop new antiepileptic medications. Ongoing surgical trials promise to evaluate the efficacy of the prevention of stroke.

Mr. Conte. Are you ready to implement clinical trials for any of these?

Dr. Goldstein. Yes, we have several clinical trials that were approved but could not be initated in FY 1990. These include two new treatments for multiple sclerosis; a clinical trial of enzyme replacement therapy for Gaucher's disease to build on the intramural work on this treatment; a trial of medical treatment for secondary stroke prevention; a study of surgical treatment for seizures; and a study of a drug treatment for status epilepticus.

We have six new trials in the planning process that could be considered for initiation in FY 1991. These include a treatment for head injury and a treatment for spinal cord injury. We would also support the National Acute Spinal Cord Injury Study III. Two other trials would determine the efficacy of a calcium channel blocker and another anticonvulsant to treat patients with partial seizures. Finally, we also would conduct a trial of monoclonal antibodies to treat multiple sclerosis. As with the six trials we could not start in 1990, these six trials will not be able to be initiated in FY 1991 within the present budget request.

HUNTINGTON'S DISEASE

Mr. Conte. Where do we stand in the search for the gene that causes Huntington's disease?

Dr. Goldstein. The search for the Huntington disease (HD) gene is continuing. A variety of high resolution genetic and physical mapping techniques have narrowed the region for the HD gene to a small zone in the terminal end of the short arm of chromosome 4. Recent studies have indicated that a more internal locus for the gene must also be considered. The study of these loci is the subject of intense investigation and may elucidate the unusual nature of the genetic material at the tips of chromosomes and the nature of genetic recombination.

Utilizing new markers, the presymptomatic test for HD is now estimated at 99 percent accurate when tissues from sufficient family members are available for study. The Venezuelan pedigree of HD families continues to contribute significantly to investigations of HD. It has been observed that HD patients with onset of illness at a young age usually inherit the gene from their fathers. This suggests that a protective factor may be conveyed when the HD gene is inherited from the mother. Genes for cellular structures known as mitochondria have been ruled out as the cause of the maternal protective effect. Other possible mechanisms are being studied.

Mr. Conte. Are there any new drugs being considered or evaluated that would slow the progression of Huntington's?

Dr. Goldstein. Drugs that block the destructive effects of quinolinic acid, a naturally occurring neurotoxin, are being tested for their cell protection properties in tissue culture and in rats.

HUMAN GENOME PROJECT

Mr. Conte. With all your work in genetic therapy and research, in what ways are you working with the new National Center for Human Genome Research?

Dr. Goldstein. The NINDS's Laboratory of Molecular and Cellular Neurobiology is one of the few laboratories in the world which can conduct large scale DNA sequencing of neurotransmitter receptor genes and human chromosomal regions to which neurological disorders with a genetic basis have been mapped. As part of its ongoing projects, it has been developing sequencing strategies and technologies which will allow the sequencing of very large regions of DNA in a highly efficient manner. Because of this, the National Center for Human Genome Research is considering collaborating with the NINDS to sequence the X chromosome which contains the genetic material believed to be implicated in many neurogenetic disorders, including one form of muscular dystrophy.

ALZHEIMER'S DISEASE

Mr. Conte. What major projects are underway that look at the genetic and other possible causes of Alzheimer's disease?

Dr. Goldstein. In an autosomal dominant subgroup of familial Alzheimer's disease cases, NINDS intramural scientists are investigating genetic linkage to identify the primary molecular abnormality underlying the disease process. Currently, they are working with 18 families that have the autosomal dominant pattern of inheritance; more than 250 family members have been examined. This is part of an international collaboration involving families from the United States, Canada, Italy, France, and Germany which was organized and coordinated by NINDS scientists.

Other areas of intense research emphasis in the NINDS are studies of the biological basis of the disease, including modern approaches to the pathology and chemistry of the disease, programmed nerve cell death and death due to viral infections and toxins, and studies of animal models for the disease process. The Institute also supports studies that will lead to more refined diagnostic and prognostic tools, information regarding the natural history of the disorder, and clinical-pathological correlations.

Mr. Conte. Are you collaborating with the National Institute on Aging in investigating Alzheimer's Disease?

Dr. Goldstein. Yes. An interagency agreement between the NINDS and NIA provides support for the establishment of skin fibroblast and blood lymphoblast cultures from families with familial Alzheimer's disease.

Also, the staffs of this Institute and the National Institute on Aging interact regularly to assure that grant proposals of highest quality are supported and duplication of efforts is avoided. In areas of mutual interest, program announcements are issued jointly and grant proposals are dually assigned. Representatives of these Institutes and others meet monthly in the NIH Coordinating Committee on Alzheimer's Disease. Representatives of each Institute also interact in the DHHS Council on Alzheimer's Disease.

BATTEN'S DISEASE

Mr. Conte. What has the Institute done in the past year to improve Batten's disease research?

Dr. Goldstein. In FY 1989 the NINDS provided funding for three research projects on Batten's disease. Work with animal models has provided insight regarding intracellular events occurring in the disease. The NINDS also supports a substantial number of basic research projects that promise to provide new information about both the fundamental workings of the developing nervous system, and the sequencing of genetic materials; these will undoubtedly result in improved leads to an understanding of Batten's disease. In addition to our extramural efforts, selected patients are seen at the Clinical Center in Bethesda as part of the research program in the NINDS Developmental and Metabolic Neurology Branch. To stimulate more interest in Batten's disease research, the Institute has repeatedly published program announcements soliciting the submission of grant applications on Batten's disease specifically and on the ceroid-lipofuscinoses which include Batten's disease. NINDS also continues to publicize its interest in national journals and at national scientific meetings. In addition, the Institute provided support for the International Conference on Ceroid-Lipofuscinosis to be held May 30-June 1 of this year.

RESEARCH CENTERS

Mr. Stokes. Your budget request for centers is for level funding of 29 research centers at $22.2 million. At this level, would you reduce the number of centers or would you drastically cut funding for existing centers?

Dr. Goldstein. We plan to fund the same number of centers in FY 1991 as in FY 1990 but there will be downward negotiations on the awards made.

Mr. Stokes. In your professional judgment, at what level should these centers be supported?

Dr. Goldstein. The professional judgment budget for the 29 centers would be $27,122,000.

STROKE

Mr. Stokes. In your opening remarks, you stated that the incidence of stroke is now rising, but you do not know why. You also stated that even low birthweight infants suffer mortality and morbidity resulting from brain hemorrhage. Please quantify this increase in incidence for us.

Dr. Goldstein. In a large population study in Rochester, Minnesota, the average annual incidence rate of stroke declined by 46 percent between 1950 and 1979. The rates stabilized in the 1970s. For the period of 1980-1984, the incidence rate of stroke was 17 percent higher than that for 1975-1979. (The data for 1985-1989 are not yet available.) The data available suggest that the incidence of stroke is now rising.

NEWBORN BRAIN HEMORRHAGE/LOW BIRTHWEIGHT

Mr. Stokes. How common is brain hemorrhage in low birthweight babies? Do you have any clue as to why this occurs?

Dr. Goldstein. The incidence of intracranial brain hemorrhage in low birthweight babies ranges from an estimated 35-50 percent. The hemorrhage in the brain is believed to occur when stresses in the extrauterine environment markedly alter the cerebral blood pressure and flow. These alterations are thought to result in hemorrhage which begins within the delicate capillary network of a specific area of the immature brain called the germinal matrix. The hemorrhage may progress to massive bleeding into the ventricles of the brain.

STROKE

Mr. Stokes. How much is requested in the FY 1991 budget for stroke research? How does this compare to FY 1990?

Dr. Goldstein. The FY 1991 budget request contains an estimated $48,496,000 for stroke research. This is an increase of $2,134,000 or a 4.4 percent increase over FY 1990.

NEW AND COMPETING GRANTS

Mr. Early. What percentage of new & competing grants will be funded under the FY91 budget request? How does this compare to FY90 and FY89? When was the last time you had this award rate?

Dr. Goldstein. The estimated percentage of new and competing grants to be funded under the FY 1991 budget request is 26.6 percent. The rate for FY 1989 was 33.7 percent and FY 1990 is projected to be 31.4 percent. Historically, the NINDS competing grant award rate has never dropped below 30 percent.

Mr. Early. How many new and competing grants will you be funding under this budget request? And how does that compare to FY '90 and FY '89?

Dr. Goldstein. The number of new and competing project grants to be funded in FY 1991 was indicated to be 405 in the FY 1991 budget request. This would require a reduction in funding of 25 percent for almost all competing research project grants. Since a 25 percent cut in the budget of a research project might prevent the investigator from meeting the objectives of the approved research project, we are proposing to reduce the number of competing research project awards to 354 in 1991 which would maintain a budget reduction for each project at 12 percent. For FY 1990, NINDS is currently applying a reduction of 12 percent in lieu of the 17 percent originally estimated. As a consequence, this adjustment resulted in a reduction in the number of competing grants that will be supported in FY 1990; the number awarded in FY 1990 will be 415 instead of 471 originally estimated. For FY 1989, the number of new and competing research project grants was 493.

Mr. Early. To what payline percentile will you fund under this request, and how does this compare to the past two fiscal years? Give us an idea of what the priority score would be?

Dr. Goldstein. The payline percentile that will be funded under the FY 1991 budget request is 19. In FY 1990 it was 17 and in FY 1989 the payline percentile was 30.1. Although payline percentiles have replaced the use of priority scores as of 1989, an estimate of the payline priority score for FY 1991 would be 150.

RESEARCH CENTERS

Mr. Early. You plan to fund 29 research centers in FY91, the same as in FY90, with the same amount of funding. This is slightly less than the amount expended in FY89 to support 29 centers. How does this downward negotiation rate compare to FY '90 and FY '89?

Dr. Goldstein. In FY 1989, the downward negotiation rate for research centers was 8.2 percent as compared to the rate of 16.6 percent estimated for FY 1990 and 18 percent estimated for FY 1991.

Mr. Early. What are the downward negotiations for non-competing centers, for competing centers?

Dr. Goldstein. The downward negotiations for non-competing centers and competing centers in FY 1991 is estimated to be 18 percent.

Mr. Early. What effect will another year of large downward negotiations have on the centers and their research programs?

Dr. Goldstein. Research studies in some of the centers will have to be limited in scope, delayed or terminated. Reductions in patient accession/retention rates in terms of the planned number required to conduct clinical studies have already occurred in some centers and these reductions will cause a delay in accomplishing the research and obtaining the research results.

Mr. Early. Doctor, is it true that NINDS is capping the amount of the grant award to centers?

Dr. Goldstein. Yes, we have just begun to phase in a ceiling for all new and competing applications for centers as well as program project grants.

Mr. Early. What is that cap and how will it be determined? Is it a fixed amount?

Dr. Goldstein. A ceiling of $750,000 (direct cost) has been established for all new and competing center applications. Support for each subsequent year of funding will also be limited to this ceiling.

Mr. Early. What is the rationale for taking this action?

Dr. Goldstein. In order to be able to fund more individual investigator initiated grants and control the cost of the grants funded, we have decided to impose a ceiling on all new and competing center and program project grants.

Mr. Early. Is there any scientific basis for taking this action?

Dr. Goldstein. No, there is no scientific basis for taking this action. However, we feel it is more advantageous to make more funds available for individual investigator awards.

Mr. Early. What effect will this cap have on the ongoing research at these centers?

Dr. Goldstein. As investigators come in with their new and competing applications subject to the $750,000 cap, we expect that they will have to eliminate some research studies and limit the scope of their work to remain under the cap.

Mr. Early. What is the estimated full cost for research centers in FY91?

Dr. Goldstein. The estimated full cost for the centers in the budget is $27,122,000.

Mr. Early. For the record provide a list of all your centers. Indicate the type of center, the estimated FY90 & FY91 funding level for each, and whether it is up for renewal in FY90 or FY91.

Dr. Goldstein. A list of the research centers with estimated total cost follows:

Research Centers FY 1990-1991 Estimates

Principal Investigator, Institution Location, Project Title	FY 1990 Estimate	FY 1991 Estimate
Pullarkat, Raju K. Institute for Basic Research in Developmental Disabilities New York, New York Neurogenetic Disorders of Infancy and Childhood * Extended without funds in FY 1990 Competing in 1991	--- *	---
Watkins, John B. Children's Hospital of Philadelphia Philadelphia, Pennsylvania Pathogenesis of Reye's Syndrome Competing in 1991	$828,447	---
Weiner, Norman University of Colorado Health Sciences Center Denver, Colorado Basal Ganglia Disorders and Neurotransmitter Function (Parkinson's Disease) Competing in 1991	602,849	---
Davis, James N. Duke University Durham, North Carolina Duke-V.A. Center for Cerebrovascular Research Competing in 1992	650,958	$676,996
Toole, James F. Wake Forest University Winston-Salem, North Carolina Cerebrovascular Research Center Competing in 1991	470,484	---
Whisnant, Jack P. Mayo Foundation Rochester, Minnesota Cerebrovascular Clinical Research Center Competing in 1991	810,231	---

Principal Investigator, Institution Location, Project Title	FY 1990 Estimate	FY 1991 Estimate
Reivich, Martin University of Pennsylvania Philadelphia, Pennsylvania Cerebral Blood Flow and Metabolism in Stroke and Shock Competing in 1990 (May Council)	---	---
Price, Thomas R. University of Maryland at Baltimore Baltimore, Maryland Clinical Stroke Research Center Competing in 1990 (May Council)	---	---
Wu, Kenneth K. University of Texas Health Science Center Houston, Texas Prostaglandins in Cerebrovascular Thrombosis Competing in 1993	760,586	791,009
Mattson, Richard H. Yale University New Haven, Connecticut Yale Epilespy Research Center Competing in 1991	983,497	---
Kellaway, Peter A. Baylor College of Medicine Houston, Texas Epilepsy Research Center Competing in 1992	1,217,810	1,266,522
Prince, David A. Stanford University Stanford, California Epilepsy Research Program Competing in 1991	987,667	---
Ferrendelli, James A. Washington University Saint Louis, Missouri Basic Mechanisms of Seizures (Epilepsy) Competed in 1990	762,351	792,845
Gumnit, Robert J. University of Minnesota of Minneapolis-Saint Paul Minneapolis, Minnesota Minnesota Comprehensive Epilepsy Program Competing in 1991	996,072	---

Principal Investigator, Institution Location, Project Title	FY 1990 Estimate	FY 1991 Estimate
Dement, William C. Stanford University Stanford, California Center for Narcolepsy and Related Disorders Competing in 1994	1,003,566	1,043,709
Johnson, Kenneth P. University of Maryland at Baltimore Baltimore, Maryland Amyotrophic Lateral Sclerosis and Multiple Sclerosis Center Grant Competing in 1992	396,077	411,920
Koprowski, Hilary Wistar Institute of Anatomy and Biology Philadelphia, Pennsylvania Etiology and Pathogenesis of Multiple Sclerosis Competing in 1993	1,075,046	1,118,048
Oldstone, Michael B. Scripps Clinic and Research Foundation La Jolla, California Multiple Sclerosis and Amyotrophic Lateral Sclerosis Pathogenesis Competed in 1990	764,036	794,597
Roos, Raymond P. University of Chicago Chicago, Illinois Motor Neuron Disease Center Grant (Amyotrophic Lateral Sclerosis) Competing in 1993	819,185	707,048
Pleasure, David E. University of Pennsylvania Philadelphia, Pennsylvania Studies of Neuromuscular Diseases Competing in 1991	762,142	---
Fields, Bernard N. Harvard University Boston, Massachusetts The Molecular Basis of Viral Injury to the Nervous System Competing in 1992	618,865	643,620

Principal Investigator, Institution Location, Project Title	FY 1990 Estimate	FY 1991 Estimate
Griffin, Diane Johns Hopkins University Baltimore, Maryland Demyelinating Diseases of the Nervous System Terminates in 1990	---	---
Cermak, Laird S. Boston University Boston, Massachusetts Brain-Injury Memory Disorders Research Center Competing in 1992	500,512	520,532
Young, Wise New York University New York, New York Clinical Research Center for Acute Spinal Cord Injuries Competed in 1990	726,491	755,551
Hunt, William E. Ohio State University Columbus, Ohio Spinal Cord Injury Research Center Competing in 1992	935,105	972,509
Collins, William F., Jr. Yale University New Haven, Connecticut A Center for Acute Spinal Cord Injury Competing in 1992	590,087	477,921
Bigner, Darrell D. Duke University Durham, North Carolina Malignant Human Gliomas and Medulloblastoma Competing in 1994	1,034,115	1,075,480
Bates, Elizabeth University of California San Diego San Diego, California Center for the Study of the Neurological Basis of Language Competing in 1990 (May Council)	---	---
Poletti, Charles E. Massachusetts General Hospital Boston, Massachusetts Face and Head Pain: Experimental and Clinical Studies Terminates in 1990	---	---

CLINICAL TRIALS

Mr. Early. Will you start any new clinical trials in FY91? If so, which ones and what is the associated cost?

Dr. Goldstein. There are no new clinical trials planned to be funded from the FY 1991 budget request.

Mr. Early. Are there any high priority clinical trials which are ready but cannot be initiated because of the lack of funds in the FY91 request? If so, please provide a list of these, along with a brief description and the associated costs, including first year cost.

Dr. Goldstein. There are six new clinical trials ready to be funded in FY 1991 if additional funds were available. They are as follows:

Clinical Trials Ready to Begin in FY 1991
if Additional funds were Available

Title	Estimated First Year Cost	Total Projected Cost
Pegolated superoxide dismutase (PEG-SOD) in the treatment of traumatic head injury	$1,000,000	$5,000,000
National Acute Spinal Cord Injury Study III	1,000,000	5,000,000
TRH (thyroxin releasing hormone) in the treatment of traumatic spinal cord injury	750,000	3,750,000
Monoclonal antibody treatment of multiple sclerosis	500,000	1,500,000
Efficacy trial of a calcium channel blocker in patients with partial seizures	500,000	1,000,000
Efficacy trial of an anticonvulsant in patients with partial seizures	300,000	750,000
Total	4,050,000	17,000,000

Mr. Early. Doctor, will you have to curtail any ongoing clinical trials with your FY91 budget request? If so, which ones?

Dr. Goldstein. There are no plans to curtail any ongoing clinical trials in FY 1991.

Mr. Early. Which mechanisms are the most commonly used to support clinical trials?

Dr. Goldstein. Most of our clinical trials are supported by research project grants. Other mechanisms used to support clinical trials include centers, R&D contracts, and intramural research.

CLINICAL RESEARCH

Mr. Early. How does NINDS support clinical research?

Dr. Goldstein. Our clinical research program is supported by all the extramural mechanisms including research project grants, centers, other research grants, the National Research Service Awards, contracts, and by the Division of Intramural Research.

Mr. Early. Is the clinical research generally more costly? Briefly explain the major reasons for this.

Dr. Goldstein. Clinical research is generally more costly to conduct because of the involvement of human patients and the special needs and safeguards associated with their care. Additionally, in order to achieve a statistically valid result it is frequently necessary to enroll a large number of patients (including normal controls for comparison), and to involve a number of different cooperating institutions, thus adding to the cost.

Mr. Early. To what extent are the downward negotiations having an adverse effect on clinical research at your institute?

Dr. Goldstein. The major impact that downward negotiations have had on clinical research studies is that the reduced funding levels have caused the number of patients enrolled in studies to be reduced from the planned number. A reduction in the size of the patient study group could force the extension of the study in an attempt to strengthen the validity of the data or else the study results could be determined to be statistically invalid. Major cuts in funding levels also mean that some aspects of the study would have to be delayed or eliminated from the study. These reductions will translate into less utilization of the more advanced technologies/techniques in fewer studies. While the larger clinical trials have been protected from cuts, it is not possible to avoid reductions in all projects involving clinical studies.

RESEARCH CAREER AWARDS

Mr. Early. The budget request indicates that NINDS will support 207 research career awards, an increase of 18 over the FY 90 level. What are your plans here?

Dr. Goldstein. The FY 1991 request for research career awards reflects the continuing commitment of the NINDS to preparing young investigators, particularly clinical investigators, for careers in research related to neurological disorders. Within the research career awards category, priority is given to the Clinical Investigator Development Awards (CIDAs). Our usual practice is to award 30 new CIDA awards and 15 new Research Career Development Awards (RCDAs) each year.

ADDITIONAL FUNDS

Mr. Early. If an increase over your FY91 budget request is provided, how would you use these additional funds? For the record, please be as specific as possible.

Dr. Goldstein. The highest priorities for NINDS in FY 1991 are to expand the research effort in head injury as recommended by the Interagency Head Injury Task Force; to initiate clinical trials of interventions ready for clinical evaluation; to increase research on neurogenetic and developmental disorders; to restore cuts planned for new and continuing projects and centers; and to increase the number of competing project grant awards.

Full implementation of a program of regional head injury research centers would require approximately $15 million in the first year. This figure is based on establishment of five centers at $2 million each, and the support of another $5 million in research project grants.

A portion of any increase would go towards increasing the Institute's research program in neurogenetic diseases. An expanded neurogenetics program would cost an additional $14.6 million.

Clinical trials that would be funded in FY 1991 if funds were available include one trial dealing with treatment of head injury, two in spinal cord injury, one for treatment of multiple sclerosis, and two studies of drugs for the treatment of epilepsy. The first-year cost would be $4.05 million; total cost is $17 million over a period of five years.

FUNDING FOR NEW RESEARCH INITIATIVES

Mr. Early. Will any significant new research initiatives or opportunities be lost or delayed due to lack of funds in the FY91 request?

Dr. Goldstein. The FY 1991 funding level will not allow for the expanded efforts in head injury, neurogenetic diseases, and clinical trials warranted by the scientific opportunities in these areas. The FY 1991 budget request is based on a 25 percent reduction in competing grant budgets; we are recommending a 12 percent reduction with fewer competing awards. Either or both of these reductions will effectively postpone or eliminate the pursuit of a substantial number of scientific opportunities.

Mr. Early. Please provide, for the record, a list of these along with a brief description and the funding requirements associated with each.

Dr. Goldstein. The following clinical trials would be funded in FY 1991 if additional funds were available:

Clinical Trials Ready to Begin in FY 1991
if Additional funds were Available

Title	Estimated First Year Cost	Total Projected Cost
Pegolated superoxide dismutase (PEG-SOD) in the treatment of traumatic head injury	$1,000,000	$5,000,000
National Acute Spinal Cord Injury Study III	1,000,000	5,000,000
TRH (thyroxin releasing hormone) in the treatment of traumatic spinal cord injury	750,000	3,750,000
Monoclonal antibody treatment of multiple sclerosis	500,000	1,500,000
Efficacy trial of a calcium channel blocker in patients with partial seizures	500,000	1,000,000
Efficacy trial of an anticonvulsant in patients with partial seizures	300,000	750,000
Total	4,050,000	17,000,000

An expanded head injury research program of the magnitude recommended by the Task Force would cost an additional $15 million in the first year. Also, an expanded neurogenetic and developmental disorders research program would cost an additional $14.6 million.

Mr. Early. Doctor, will any significant research initiatives currently underway be halted or seriously delayed due to FY91 funding levels?

Dr. Goldstein. FY 1991 funding levels will have a major impact on the level of activity in the positron emission tomography (PET) centers. Some projects, such as those dealing with the mechanisms of addiction on the brain, will not be continued. The four Javits Centers of Excellence awards will be terminated as the initial awards expire this year; new applications are not being sought. In taking this action, we recognize that we lose the unique multidisciplinary environment of the Javits Centers which have already fostered productive and creative investigations. The centers were designed so small groups of investigators--the most outstanding and innovative groups in the country--could work collaboratively on fundamental issues in nervous system structure and function.

Other research efforts, because of their special characteristics, are being given special consideration. In particular, clinical trials have been protected because the nature of the studies requires a certain number of patients and duration of follow-up in order to obtain valid results. We have also made special provision for the research career awards in order to ensure a continued infusion of new research talent, especially in clinical areas.

Mr. Early. To what extent will there be major reductions in the scope of ongoing or new initiatives because of the FY 91 funding levels?

Dr. Goldstein. The resources available in the FY 1991 request limit the number and amount of competing project grants that may be awarded. If the Institute were to fund the 405 competing grants identified in the FY 1991 budget request, it would be necessary to reduce nearly all of them by 25 percent. In the professional judgment of NINDS staff, this level of reductions would prevent funded investigators from meeting the objectives of the approved research project. For the current year, NINDS is applying a reduction of 12 percent in lieu of the 17 percent originally estimated with a concomitant reduction in the numbers of grants to be awarded (415). This has permitted the research presently active to continue, but at a substantially reduced level of productivity. For this reason NINDS will recommend reducing the number of competing research project awards to 354 in 1991 in order to maintain the present budget reduction for each project at 12 percent.

In an effort to maintain the current numbers of centers and program projects, the NINDS has just begun to phase in a $750,000 ceiling for new and competing grant applications. This action will translate into utilization of PET technology in fewer studies. Plans to expand the use of PET to studies of various neurotransmitters, and studies of patients with Alzheimer's disease, Parkinson's disease, cognitive brain disorders, learning disabilities, drug and alcohol addiction, and movement disorders are on hold.

PROFESSIONAL JUDGMENT BUDGET

Mr. Early. What was your professional judgment budget request for FY91, including the AIDS funds and excluding them?

Dr. Goldstein. The FY 1991 professional judgment budget is $691,421,000 with AIDS funds included. Without the AIDS funds the budget is $662,773,000.

Mr. Early. In which areas did it differ from the request now before the committee?

Dr. Goldstein. The FY 1991 professional judgment budget is $179,209,000 more than the FY 1991 request of $512,212,000.

Specific areas where the FY 1991 professional judgment budget is more than the FY 1991 request include noncompeting research projects for $50,184,000; 280 competing research project grants for $72,275,000; 19 research centers for $22,379,000; 48 research career development program awards for $3,859,000; 3 cooperative clinical research grants for $4,502,000; other research grants, 37 grants for $2,166,000; 64 individual NRSA trainees for $1,968,000; 113 institutional NRSA trainees for $3,093,000; 35 R&D contracts for $10,209,000; intramural research, 47 FTEs and $5,746,000; and research management and support, 17 FTEs and $2,828,000.

RESEARCH TRAINEES

Mr. Early. The FY 90 bill provided for a significant increase in the number of research trainees over FY 89 level. However, the number of research trainees at your institute declines. Doctor, would you explain why?

Dr. Goldstein. The number of NINDS research trainees has declined slightly due to increased cost of training grants and the reduction of funds resulting from sequestration.

HUNTINGTON'S DISEASE

Mr. Early. What advances have been made in the area of Huntington's disease within the past year or so?

Dr. Goldstein. We continue to make progress in identifying the location of the Huntington's disease (HD) gene and understanding the etiology of the disease. The major effort utilizes a variety of high resolution genetic and physical mapping techniques which have narrowed the region for the HD gene to a small zone in the terminal end of the short arm of chromosome 4. A second group is exploring another possible locus that has recently been postulated. Utilizing new markers, the presymptomatic test for HD is now estimated as 99 percent accurate when tissues from sufficient family members are available for study.

Cultured cells from people with two copies of the HD gene (homozygotes) have been exceptionally valuable in the cloning strategies used to pursue the HD gene because there is no normal gene to confound the results. A yeast artificial chromosome containing the terminal 100 kilobases of chromosome 4 from an HD homozygote was constructed. This accomplishment holds promise for isolating the defective gene.

The Venezuelan pedigree of HD families continues to contribute significantly to investigations of HD. It has been observed that HD patients with onset of illness at a young age usually inherit the gene from their fathers. This suggests that a protective factor may be conveyed when the HD gene is inherited from the mother. Genes for cellular structures known as mitochondria have been ruled out as the cause of the maternal protective effect. Other possible mechanisms are being studied.

The metabolism of quinolinic acid is greatly increased in HD, yet the absolute concentrations of this naturally occurring neurotoxin are unchanged from normal brain. Recent studies indicate that the NMDA (N-methyl-D-aspartate) receptor may be involved in the cellular destruction seen in this disease. This work has greatly stimulated the search for new protective drugs which bind at this receptor. Preliminary results have shown that fibroblast growth factor protects the cells from NMDA toxicity. Other studies show certain subclasses of the same cell type destroyed in HD may be differentially spared depending upon the neurotransmitters they contain.

DECADE OF THE BRAIN

Mr. Early. The justification indicates that the Office of Science and Technology is developing a plan to implement the Decade of the Brain. What does this entail? When will the plan be ready?

Dr. Goldstein. The Committee last year directed the Office of Science and Technology Policy (OSTP) to constitute a panel for developing an implementation plan for the Decade of the Brain. As a first step, OSTP has convened a working group to recommend strategies for developing a coordinated plan and to suggest membership for the panel. The group has met twice and includes representatives of all NIH and ADAMHA institutes concerned with brain research, as well as the National Science Foundation, the Department of Veterans Affairs, and the Department of Defense; representation from additional agencies will be sought. The timetable for the plan will depend on the appointment of the panel by the OSTP and the approach selected. The Panel will have the opportunity to review the plans of the various agencies and propose an integrated national effort for the Decade of the Brain. In the interim, the OSTP working group provides a forum for exchange among the various agencies.

HEAD INJURY AND SPINAL CORD INJURY

Mr. Early. What recent advances have there been in research on head injury and spinal cord injury?

Dr. Goldstein. We are very pleased to report that we have, for the first time, a drug treatment for acute spinal cord injury. A clinical trial supported by the NINDS, the second National Acute Spinal Cord Injury Study, is now complete and the results offer great promise for the prevention of paraplegia after spinal injury. Eleven centers participated and enrolled over 400 patients to test the effectiveness of naloxone and high dose methylprednisolone given within hours after acute spinal cord injury. Statistical evaluation of data taken at six weeks and six months after injury indicated a significant improvement in neurological outcome in patients treated with methylprednisolone.

Recent work has shown that the nervous system produces factors that inhibit the growth of nerve fibers in addition to growth promoting factors. In studies of experimental spinal cord injury, treatment of laboratory animals with antibodies to one type of "anti-growth" factor resulted in extensive elongation of injured nerve tracts. The identification of other such factors and creation of other treatment strategies to maximize regeneration is underway.

One of the most exciting new areas of laboratory investigation for potential treatment for central nervous system trauma is the use of immature nervous tissue to replace damaged areas of the adult brain or spinal cord. The feasibility of implantation has been established in animal studies. Research is now aimed at understanding the interactions of the host nervous system and the implanted tissue, demonstrating the long-term survival and growth of the implants, and critically assessing the potential of the grafts to restore lost function. In addition, investigators have shown that it is possible to genetically engineer cells to produce specific factors or transmitters that are deficient in certain neurological conditions or after specific lesions. These cells can then be implanted to serve as biological "mini-pumps" to provide the missing factors. More work needs to be done before this technique has widespread use, however.

It has now been shown that implanted peripheral nerve structural elements--consisting of the Schwann cells and perhaps other cellular elements--can guide regenerating central axons for long distances. Recently, investigators demonstrated that these regenerated axons were capable of establishing appropriate, functional synapses in the correct target regions of the brain. This holds out the real possibility of functional return after injury to the central nervous system.

MULTIPLE SCLEROSIS

Mr. Early. Have we made any further progress in the area of multiple sclerosis?

Dr. Goldstein. We know that autoimmune reactions against the myelin sheath of nerve cell fibers is an important factor in the pathogenesis of this common, chronic, neurologic disease. There is evidence that genetic, viral and immune factors are involved in contributing to disease development. In recent years, studies of immunological abnormalities found in multiple sclerosis (MS) patients received special attention because of the important role that immune abnormalities seem to play in multiple sclerosis, and because the immune system can be modulated with drugs in an attempt to develop effective treatment of the disease. We have learned that sensitized T cells can become cytotoxic, and that they can release factors which activate macrophages. Activated macrophages in turn may secrete enzymes which could damage and destroy myelin. Newly formed antibodies in the presence of activated complement can also become toxic to myelin, and can damage the blood brain barrier. Recent advances in our knowledge of the nature of the T cell receptor, and demonstration that blocking the receptor may successfully prevent an experimental disease which serves as an animal model of MS, have opened new approaches for potential clinical application.

COST OF MAJOR NEUROLOGICAL DISORDERS

Mr. Early. The majority of diseases and disorders that NINDS supports research for are characterized by long-term disabilities. We would sure save a lot of money if we could find the cause and cure for many of these, wouldn't we doctor?

Dr. Goldstein. Yes, we would. In 1989 the cost of illness associated with the major neurological disorders on which NINDS supports research was $98.205 billion. This includes direct cost of health care as well as indirect costs of income lost due to illness.

JOSEPH DISEASE

Mr. Early. Doctor, what is Joseph disease and what do we know about its cause and how to prevent and treat it?

Dr. Goldstein. Joseph disease is an autosomal dominant hereditary motor system disease seen primarily among families from Portuguese ancestry. Its symptoms appear in the second and third decades of life. Intellectual function is spared. The progressive neurologic deficits result in death from debilitation within 10 to 30 years of onset. Joseph disease is believed to be caused by a single gene mutation on chromosome 1, the expression of which is modified by other genes resulting in some variation of clinical symptoms. The defective gene product coded for by the gene mutation is not known. Thus, there is no effective treatment or cure. At present, prevention depends on genetic counseling of identified families.

Mr. Early. What research on Joseph disease is being supported by NINDS?

Dr. Goldstein. The NINDS supports an active research portfolio relevant to understanding the basic genetic, biochemical and physiological defects associated with inherited neurological diseases. For example, a possible defect of the enzyme, glutamate dehydrogenase, is being studied in patients with Joseph disease as a potential metabolic clue to the pathophysiology of this disease.

Mr. Early. Can you tell me what resources are being allocated to research in this area and what your program plans are for FY 91?

Dr. Goldstein. In fiscal year 1989, NINDS spent $51,000 on research directly related to Joseph disease, and $11 million on related neurogenetic neurological research. NINDS is encouraging research grant applications in the area of neurogenetic disorders, particularly in areas of clinical research. In addition, in an effort to reaffirm a strong commitment to basic research in neurogenetics, NINDS jointly sponsored with the National Institute of Child Health and Human Development a research grant program announcement in "Molecular and Developmental Neurobiology."

Mr. Early. How would you describe the state of the science in this area? What are some of the key questions that need to be answered in order to make more progress in this area?

Dr. Goldstein. At the present time basic knowledge on molecular genetic techniques exists which needs to be applied to specific cases of Joseph disease. Scientists have developed diagnostic criteria for the several forms of Joseph disease. It is postulated that all forms of Joseph disease can be attributed to a defective gene product encoded on chromosome 1 and that clinical variation can be attributed to the modifying influences of other genes. To answer some key questions, several approaches are needed: studies of large family pedigrees to confirm and more precisely define the locus of the genetic defect; and application of "reverse genetic" techniques to identify the defective gene product(s). Until at least a genetic marker can be identified, genetic counseling is very limited.

Mr. Early. Are other institutes supporting research that has implications for addressing this disorder?

Dr. Goldstein. The National Institute of General Medical Sciences is funding research in the basic science of molecular genetics. The National Institute of Child Health and Human Development is funding research in the basic science of neurogenetics.

Mr. Early. Are there additional steps the institute could take to encourage greater efforts in this area?

Dr. Goldstein. The NINDS is committed to encouraging scientific interest in neurogenetic disorders through its programmatic leadership and by encouraging promising and outstanding investigators to undertake studies of complex and rare disorders such as Joseph disease. The NINDS could issue a program announcement on Joseph disease to stimulate submission of research grant applications. Subject to the availability of funds, a specific Request for Applications (RFA) could be issued to establish a research center to study Joseph disease and related genetic disorders.

TRAUMATIC BRAIN INJURY

Mr. Dwyer. Recent studies of inmates on death row concluded that many of these men and women were abused as children, most suffering severe blows to the head. Has the NINDS been working with the National Institute on Mental Health to determine the relation between antisocial and criminal behavior and traumatic brain disorder?

Dr. Goldstein. Regardless of the degree of brain injury, subtle to extensive neuropsychological and psychiatric consequences may ensue. Several of the recommendations of the Interagency National Head Injury Task Force, which included representatives of the National Institute of Mental Health and the NINDS, related to establishing and developing an understanding of the dysfunctional and behavioral, cognitive, and emotional responses and sequelae of brain injury. This would be relevant to understanding the effects of brain injury resulting from child abuse.

HEAD INJURY

Mr. Dwyer. What treatments are being developed for physiological disturbances after head injury?

Dr. Goldstein. Investigators are approaching the treatment of physiological disturbances in the injured brain from many directions. Surgical intervention to reduce increased intracranial pressure and a more comprehensive assessment of cerebral perfusion pressure as it relates to blood pressure and intracranial pressure are directly relevant to the management of acute traumatic brain injury. Similarly, better assessment of cerebral blood flow after head injury would allow better evaluation of cerebral ischemia (lack of oxygen); this assessment is essential because hyperventilation is often used in an attempt to supply oxygen to the brain in the acute management of severe head injury. This may in fact be unnecessary or detrimental in some patients. Data indicates that low blood flow does not necessarily correspond with ischemia.

Pharmacological agents that relate to the secondary effects of brain damage are also under investigation in randomized clinical trials. The trials are at various stages, some are still accruing patients; some analyzing data.

BRAIN DAMAGE IN CHILDREN

Mr. Dwyer. What is the estimated number of children who suffer brain damage as the result of abuse?

Dr. Goldstein. According to the Interagency Head Injury Task Force, 18,000 pediatric head injuries result annually from accidents, sports, falls, and abuse. Specifically, child abuse accounts for 64 percent of head injuries in infants.

AIDS DEMENTIA

Mr. Dwyer. A number of AIDS patients develop a dementia, which is unique to the disease. What are the symptoms of AIDS-related dementia?

Dr. Goldstein. Individuals with AIDS dementia complex have progressive cognitive impairment with behavioral and motor abnormalities. Early symptoms may be mild and consist of difficulty with concentration, performance of complex sequential mental activities, reading, or carrying out more demanding mental efforts. Intellectual functioning may be normal, except for slowness in verbal and motor responses. Later, behavioral changes may become evident including social withdrawal, apathy, personality changes, depression, or psychosis. Progressive neurological involvement can also affect gait and fine-motor movements. Late manifestations include severe cognitive impairment which may progress to mutism, seizures, and loss of some body-function controls.

Mr. Dwyer. How is AIDS-related dementia different from other dementias such as Alzheimer's Disease?

Dr. Goldstein. Alzheimer's dementia, as well as most other dementias except in AIDS, is characterized primarily by loss of memory. AIDS dementia complex is characterized primarily by subcortical involvement of which the hallmarks are slowing of movements and slowing of thinking. Deficits of memory develop late in the disease.

Mr. Dwyer. What drugs or other therapies, if any, are being used to treat this disorder?

Dr. Goldstein. In 1988 investigators reported that adult patients who received AZT experienced improvement in a wide range of cognitive functions, attention, motor skills and general brain activity when compared to a group treated with placebo. These findings were confirmed by clinical observations and nerve-conduction studies, and by positron emission tomography. In a separate study, a group of HIV-infected children showed neurodevelopmental improvement and increases in IQ scores after treatment with AZT.

EPILEPSY

Mr. Hoyer. Could you elaborate on the clinical study of new agents for the management of epilepsy mentioned in the justification?

Dr. Goldstein. Felbamate dicarbamate has proven effective in preventing seizures induced in animal models of epilepsy. Preliminary clinical studies in epileptic patients being treated with carbamazepine showed that felbamate lowered levels of that drug (presumably by an effect on its metabolic rate), but the patients did not suffer an increase in seizures. This suggested that felbamate might have had its expected antiseizure activity in addition to the effect on metabolism of carbamazepine. A trial of felbamate alone is being planned.

Mr. Hoyer. Have we actually learned anything more about the etiology, prevalence and incidence of this disorder?

Dr. Goldstein. Scientists have identified anatomical pathways and chemical substances which may be responsible for seizure spread within the brain. It is now possible to measure minute alterations in the concentration of critical chemical substances whose brain concentrations change during the initiation and propagation of a seizure. This information can lead to new drug therapy for epilepsy by permitting the design of drugs which either prevent the release of such chemicals, or block their effect upon epileptogenic receptors.

A feasibility study with a specially constructed questionnaire to determine the frequency of seizure disorders and factors associated with the development of epilepsy in urban underprivileged communities has just been completed. A full scale survey is now underway.

Mr. Hoyer. What impact has the use of magnetoencephalography had on our ability to study the effects of epileptic activity in the brain?

Dr. Goldstein. In patients with epilepsy, magnetoencephalography (MEG) is being developed to help locate abnormal brain electrical discharges to determine the site of origin of the seizure activity. Such localization studies are mandatory when surgery for epilepsy is being considered. Because present instruments provide only a few recording channels, the procedure is tedious; consequently MEG is not used routinely in the evaluation of patients being considered for epilepsy surgery. However, new technology has recently been developed for multichannel MEG recording and studies are underway which will most likely make MEG more useful for clinical use.

HEAD/SPINAL CORD INJURY

Mr. Hoyer. NINDS has established research centers at the Baylor and Boston University to study memory disorders and brain injury, and intramural researchers are working on issues surrounding brain plasticity and stroke. What have we learned about the clinical rehabilitation and basic biology of head and spinal cord injury?

Dr. Goldstein. The NINDS sponsors a number of innovative research projects that explore the use of new technology that may assist in designing rehabilitation strategies to achieve maximum benefit from the remaining functioning nervous system. An example of this is the use of magnetic resonance imaging (MRI) in the head-injured population. With MRI, additional brain lesions can be detected that would have gone undetected, and, consequently, the need for specific methods of rehabilitation can be identified. In studies of language and aphasia, investigators are using PET (positron emission tomography) to identify active areas of the brain in an effort to guide and evaluate rehabilitation strategies. PET studies of hypotonic and hypertonic phases of paralysis have been used to develop new approaches for clinical management.

Research on the long-term effects of, and recovery after, stroke and head injury reveals that the brain is functionally more dynamic than was previously believed. Neurons may be recruited from other areas of the brain to perform alternate functions, an example of which is the use of cognitive methods to control motor movement. Progress in motor-function recovery after cortical injury has been made as a result of NINDS-sponsored studies in which researchers use computerized traction tests. Animal studies of the movements of the limbs, as well as posture, have shown that some types of therapy may actually be detrimental to the regaining of locomotor function. All of this work has important implications for the restitution of function in patients with motor deficits that are the result of a stroke or other type of cortical injury.

Pioneering efforts and accomplishments important for rehabilitation are also emerging from the NINDS neural prosthesis program. Examples include studies in focal magnetic stimulation of the human central and peripheral nervous systems, neural transplantation, and implantable microstimulators for muscle stimulation.

A major problem of head-injured individuals who have overcome motor deficits is confusion and memory loss. In several Institute-sponsored projects, investigators are attempting to determine the mechanisms of this memory loss and to develop ways to deal with this debilitating problem. One NINDS contractor has developed, as a marketable product, personalized software by which head-trauma patients can be taught the mathematical, reading, and writing skills that are basic to independent living.

Many investigators believe that uninjured neurons die after trauma to the nervous system as a result of the alterations in the microenvironment surrounding these cells. Attempts to define these alterations, rectify the changes, and protect neurons from secondary damage are goals of researchers who seek efficacious treatment for head and spinal cord injury. Among the areas under investigation are the effects of anoxia, temperature, ionic concentration, and glucose on the survival of damaged neurons.

A key to future progress in neurorehabilitation is the development of research designs to evaluate which rehabilitation therapies are efficacious, under what conditions, and to which patients. Nearly all rehabilitation techniques used at this time are based on clinical experience.

Mr. Hoyer. Clearly, we need to capitalize on past efforts, but do you have any concern that tight budgets are beginning to limit our ability to foster the development of new avenues of research?

Dr. Goldstein: NINDS is making every effort to maintain the current numbers of centers and program projects. This is being accomplished by cost reductions achieved through the establishment of dollar ceilings for new and competing grant applications. The overall funding situation is discouraging some investigators from preparing and submitting research proposals for new areas of research. Funds are not available for the creation of a national network of comprehensive regional head injury research centers where multi-disciplinary research can occur. This was a key recommendation of the Interagency Head Injury Task Force, created with the encouragement of the House Committee on Appropriations, in its February 1989 report.

BATTENS DISEASE

Mr. Hoyer. The justification indicates that the genetic locus of the juvenile form of Battens Disease has been mapped to the long arm of chromosome 16. Can you elaborate on the progress we've made in the study of Battens?

Dr. Goldstein. Batten's disease, an inherited disorder, causes a buildup of fatty pigments in the brain, the nervous system, and other parts of the body. New findings from studies of an animal model of Batten's disease suggests that the disease may be related to the accumulation of a lipid-binding agent. Parallel to this work, scientists are continuing to search for the specific gene(s) responsible for the disease; with knowledge of the role of the genetic defect in causing the disease, methods of improved diagnosis, prevention, and therapy can be developed. Selected patients are also evaluated as part of the intramural research program in the NINDS Developmental and Metabolic Neurology Branch. The Institute continues to encourage new studies in Batten's disease. As part of these efforts, the NINDS will support the International Conference on Ceroid-Lipofuscinosis to be held May 30-June 1 of this year.

Mr. Hoyer. How much will we spend on Battens in FY 1990 and FY 1991?

Dr. Goldstein. Estimated support for study of Batten's disease per se is $458,000 in FY 1990 and $479,000 in FY 1991. Estimated funding for the NINDS neurogenetics program, of which Batten's disease is a part, is $69.6 million in FY 1990.

WOMEN IN RESEARCH

Mr. Hoyer. I am especially interested in the question of how will we involve women in clinical trials and other research funded by NIH, and I would appreciate your providing the committee summary information on the NINDS policy regarding the inclusion of women in clinical research and the numbers involved in on-going trials?

Dr. Goldstein. The NIH has had an announced policy for many years urging investigators to include women in the study population of all clinical research efforts. Exceptions would be studies of diseases which exclusively affect males or where involvement of pregnant women might expose the fetus to undue risks. The NINDS fully supports this policy and encourages the enrollment of women and minorities in clinical research. Total figures on the number of women in NINDS-supported clinical trials is not available because patient enrollment for many ongoing trials is not complete. However, as an example of the involvement of female patients in clinical research, 30 percent of the patient population in a recent trial on stroke prevention were women.

DYSTONIA

Mr. Porter. Please provide for the record a summary of NINDS research related to dystonia? What level of research on dystonia will the institute support in FY91? Are other institutes involved in this matter?

Dr. Goldstein. NINDS intramural investigators have achieved encouraging results with the use of botulinum toxin to treat some types of dystonia. This is an ongoing area of research to clarify dosages and explore the efficacy of different components of the botulinum toxin. The NINDS also supports research to find the defective gene(s) responsible for the inherited forms of dystonia. Progress has been made in that a genetic marker has been found in a region of chromosome 9. Identification of a dystonia gene will create numerous research opportunities to identify and characterize the gene product and develop targeted methods to prevent and treat the disease. Institute support for dystonia in FY 1991 is an estimated $1,133,600. The National Center for Research Resources also provides a modest level of support for dystonia.

CHRONIC FATIGUE SYNDROME

Mr. Porter. Does the institute support any research on Chronic Fatigue Syndrome?

Dr. Goldstein. No, we do not. Our intramural scientists have examined whether patients with Chronic Fatigue Syndrome have a primary disorder of muscle, nerve, or neuromuscular transmission which could be responsible for the chronic muscle fatigue. Our studies failed to show an organic disease of the neuromuscular system.

PARKINSON'S DISEASE/FETAL TISSUE RESEARCH

Mr. Porter. Last year Dr. Wyngaarden discussed with this committee promising research in the area of Parkinson's disease. This research involved the implantation of neural fetal tissue into monkeys with Parkinson's syndrome. How is this research progressing?

Dr. Goldstein. These experiments are progressing well in animal studies. Implants of fetal brain tissue into animal models of Parkinson's disease survive and grow, develop a blood supply, are at least partially incorporated into the host brain tissue, and in some instances form appropriate neural connections; they also reduce or reverse the Parkinson's symptoms. Using PET, the grafts have been shown to be producing the neurotransmitter dopamine. There is recent evidence that in certain instances these implants actually induce regeneration and growth of the remaining host nerves. Under the moratorium, we are unable to pursue this line of research in humans. We are attempting to find satisfactory alternate tissue. Other animal studies using preterm placental tissue suggest that there may be comparable benefits from that approach, but the results are too preliminary for human testing. Another approach, still limited to preliminary animal studies, involves genetic alteration of rat skin fibroblasts so that they secrete dopamine, then implanting those cells in the brains of rats in which dopamine-secreting cells have been destroyed. The animals respond favorably.

Mr. Porter. Has the Department's policy on the use of human fetal tissue affected research on Parkinson's? Will you be restricted from pursuing promising leads as research progresses?

Dr. Goldstein. The Department's policy has slowed progress in fetal tissue transplantation research for Parkinson's disease. The moratorium on transplantation of human fetal tissue into patients prohibits further studies which have shown promise in animal models. Investigators have chosen not to submit proposals in this research area because they are not permitted to progress to the next logical steps based upon favorable outcomes found in animal studies.

Mr. Porter. In your professional judgment, should the policy on the scientific use of human fetal tissue be modified?

Dr. Goldstein. As you know, in 1988 an expert committee was convened by the Director, NIH at the request of the Assistant Secretary for Health to consider this question. The Advisory Committee to the Director, NIH, then reviewed the report of the Human Fetal Tissue Transplantation Research Panel and recommended that the Assistant Secretary for Health lift the moratorium on Federal funding of human fetal tissue transplantation research using tissue from induced abortions. The NINDS supported that recommendation.

The Institute also recognizes the issue of using fetal tissue raises many moral questions and, therefore, supports the recommendations of the Panel that appropriate guidelines are required if this research proceeds. The guidelines would ensure that decisions involving termination of a pregnancy would be kept separate from decisions involving the use of the fetal tissue. Guidelines were also developed by the NINDS when it originally proposed human studies in the NINDS neurological research clinic at NIH.

SLEEP DISORDERS/NARCOLEPSY

Mr. Porter. Last year, the committee asked you to increase your efforts in the area of sleep disorders, especially narcolepsy, and to issue a report on your work on narcolepsy. Please provide for the status of this report, and a brief summary of NINDS research on sleep disorders.

Dr. Goldstein. The requested report on narcolepsy was transmitted to the Committee by the Secretary, Department of Health and Human Services, on February 5, 1990. The report addresses the status of current research, the activity of the Trans-NIH Sleep Research Coordinating Committee, and future research initiatives. A recently awarded NINDS center grant on narcolepsy and related disorders has as its overall direction defining the biological pathologies and exploring possible treatments. In addition, the Institute is sponsoring a workshop on narcolepsy research in cooperation with the Trans-NIH Sleep Research Coordinating Committee.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

FY 1991 Budget

Page No.

Appropriation language and explanation of language changes... 70

Amounts available for obligation.............................. 71

Budget mechanism table.. 72

Crosswalk tables.. 74

Summary of changes.. 77

Budget authority by activity.................................. 78

Budget authority by object class.............................. 79

Significant items in House and Senate Appropriations Committee reports... 81

Authorizing legislation....................................... 83

Appropriations history.. 85

Justification:

A. General statement.. 87
B. Program accomplishments.................................... 89
C. AIDS Research program...................................... 100
D. Biological Basis research.................................. 105
E. Clinical research.. 112
F. Intramural research.. 118
G. Research management and support............................ 121
H. Detail of permanent positions.............................. 122
I. Advisory and assistance services........................... 123

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

For carrying out section 301 and title IV of the Public Health Service Act with respect to neurological disorders and stroke, [$497,096,000] $512,212,000.

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1990.)

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation	$573,978,000	497,096,000	512,212,000
Enacted administrative reduction	-6,288,000	-1,471,000	---
Sequester Order	---	-5,216,000	---
Subtotal, adjusted appropriation	567,690,000	490,409,000	512,212,000
Real transfer to:			
Health Resources and Services Administration for AZT grants.	-163,000	---	---
National Institute on Deafness and Other Communication Disorders	-95,432,000	---	---
Comparative transfer to: Division of Research Resources for administrative cost of Research Centers at Minority Institutions	-18,000	---	---
Comparative transfers from: Office of the Director, NIH for increase of FTEs	+598,000	---	---
Office of Research Services to Fogarty International Center for Passport Account	-13,000	-13,000	---
Subtotal, adjusted budget authority	472,662,000	490,396,000	512,212,000
Unobligated balance lapsing	-463,000	---	---
Total, obligations	472,199,000	490,396,000	512,212,000

1/ Excludes the following amounts for reimbursable activities carried out by this account: 1989 -- $1,517,000; 1990 -- $2,961,000; and 1991 -- $3,100,000.

NATIONAL INSTUTUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Budget Mechanism
(Dollars in thousands)

	1989 Actual		1990 Appropriation 1/		1991 Estimate	
Research Grants	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting projects............	1,393	$247,460	1,395	$255,256	1,456	$287,694
Administrative supplementals.....	(7)	278	(65)	2,286	(20)	800
Competing projects:						
Competing renewals.............	213	45,860	203	46,060	174	38,346
New............................	266	37,053	254	37,297	219	31,051
Supplemental...................	14	852	14	885	12	736
Subtotal, competing..........	493	83,765	471	84,242	405	70,133
Subtotal, research projects.....	1,886	331,503	1,866	341,784	1,861	358,627
Research Centers:						
Specialized/comprehensive ctrs...	29	22,397	29	22,247	29	22,247
Subtotal, research centers.....	29	22,397	29	22,247	29	22,247
Other Research:						
Research career programs..........	189	11,964	207	13,971	207	13,971
Cooperative clinical research....	--	--	1	178	1	178
Minority Biomedical Support......	--	196	--	198	--	215
Other research related...........	81	3,470	60	2,059	59	2,049
Subtotal, other research.......	270	15,630	268	16,406	267	16,413
Total, Research Grants...........	2,185	369,530	2,163	380,437	2,157	397,287

Training						
Individual awards						
Noncompeting	64	1,571	86	2,135	100	2,684
Competing, new.................	115	2,696	85	2,384	71	1,835
Subtotal, Individual.........	179	4,267	171	4,519	171	4,519
Institutional awards						
Noncompeting	314	7,522	265	6,467	292	7,450
Competing, new.................	53	1,235	92	2,030	65	1,047
Subtotal, Institutional......	367	8,757	357	8,497	357	8,497
Total, Training.................	546	13,024	528	13,016	528	13,016
Research & Development Contracts...	38	11,604	42	11,369	42	11,381
	FTEs		FTEs		FTEs	
Intramural Research................	468	58,752	478	64,439	481	69,105
Research Management and Support....	184	19,752	187	20,079	187	21,423
Extramural Construction	--	--	--	1,056	--	--
TOTAL......................	652	472,662	665	490,396	668	512,212
HIV/AIDS....................	(40)	(13,432)	(40)	(16,158)	(40)	(17,227)

[1] Includes approximately $1,056,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

CROSSWALK - 1989 ACTUAL

(In thousands of dollars)

	Mechanism								
	Research Grants			Training Programs					
	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management and Support	Total
Biological Basis Research..........	$230,854	--	$8,126	$4,130	$5,203	$5,865	--	--	$254,178
Clinical Research....	100,649	22,397	7,504	137	3,554	5,739	--	--	139,980
Intramural Research..	--	--	--	--	--	--	58,752	--	58,752
Research Management and Support.......	--	--	--	--	--	--	--	19,752	19,752
TOTAL.............	331,503	22,397	15,630	4,267	8,757	11,604	58,752	19,752	472,662

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

CROSSWALK - 1990 APPROPRIATION

(In thousands of dollars)

	Mechanism									
	Research Grants			Training Programs						
	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management and Support	Extramural Construction	Total
Biological Basis Research..........	$238,013	--	$8,439	$4,374	$5,043	$5,745	--	--	--	$261,614
Clinical Research....	103,771	22,247	7,967	145	3,454	5,624	--	--	--	143,208
Intramural Research..	--	--	--	--	--	--	64,433	--	--	64,433
Research Management and Support.......	--	--	--	--	--	--	--	20,085	--	20,085
Extramural construction......	--	--	--	--	--	--	--	--	1,056	1,056
TOTAL.............	341,784	22,247	16,406	4,519	8,497	11,369	64,433	20,085	1,056	490,396

1/ Includes approximately $1,056,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

CROSSWALK - 1991 ESTIMATE

(In thousands of dollars)

	Mechanism								
	Research Grants			Training Programs					
	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management and Support	Total
Biological Basis Research..........	$249,743	--	$8,443	$4,374	$5,043	$5,751	--	--	$273,354
Clinical Research....	108,884	22,247	7,970	145	3,454	5,630	--	--	148,330
Intramural Research..	--	--	--	--	--	--	69,105	--	69,105
Research Management and Support.......	--	--	--	--	--	--	--	21,423	21,423
TOTAL.............	358,627	22,247	16,413	4,519	8,497	11,381	69,105	21,423	512,212

National Institute of Neurological Disorders and Stroke

Summary of Changes

1990 Estimated budget authority..................................	$490,396,000
1991 Estimated budget authority..................................	512,212,000
Net change...	+21,816,000

	1990 Current Estimate Base		Change from Base	
	Pos. (FTEs)	Budget Authority	Pos. (FTEs)	Budget Authority
Changes:				
A. Built-in:				
1. Within grade increase.........		$34,403,000		+$521,000
2. 1991 cost of January 1990 pay raise....................		34,403,000		+448,000
3. 1991 cost of January 1991 pay raise....................		34,403,000		+1,134,000
4. DHHS Working Capital Fund.....		645,000		-30,000
5. Federal Employees Compensation Fund increase...		110,000		+3,000
6. FTS rate increase.............		429,000		+14,000
7. Payment for centrally furnished services...........		23,194,000		+2,154,000
8. Service and Supply fund increase................		26,000,000		+936,000
9. One extra day of pay..........		34,403,000		+133,000
10. Unemployment compensation increase.....................		52,000		+2,000
Subtotal.................		--		+5,315,000
B. Program:				
	No.	Amount	No.	Amount
1. Research projects:				
a. Noncompeting continuations converting from competing status....................	1,395	257,542,000	+61	+30,952,000
b. Competing (new, renewals and supplementals)........	471	84,242,000	-66	-14,109,000
2. Other research grants.........	268	16,406,000	-1	+7,000
3. Research and development contracts....................	42	11,369,000	--	+12,000
	Pos. (FTEs)		Pos. (FTEs)	
4. Intramural Research...........	(478)	64,439,000	(+3)	+523,000
5. Research management and support......................	(187)	20,079,000	--	+172,000
6. Extramural construction.......		1,056,000		-1,056,000
Subtotal................		--	(+3)	+16,501,000
Total changes........		--	(+3)	+21,816,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Budget Authority by Activity
(Dollars in thousands)

	1989 Actual		1990 Appropriation 1/		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Biological Basis research............	---	$254,178	---	$261,614	---	$273,354
Clinical research.....	---	139,980	---	143,208	---	148,330
Intramural research...	468	58,414	478	64,439	481	69,105
Research management and support.........	184	19,635	187	20,079	187	21,423
Extramural construction........	---	---	---	1,056	---	---
Total, obligations....	652	472,199	665	490,396	668	512,212
Unobligated balance, lapsing.............		463		---		---
Total budget authority.........	652	472,662	665	490,396	668	512,212
HIV/AIDS..............	(40)	(13,432)	(40)	(16,158)	(40)	(17,227)

1/ Includes approximately $1,056,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Budget Authority by Object Class

	1990 Appropriation	1991 Estimate	Increase or Decrease
Total number of full-time permanent positions..............................	461	461	---
Total compensable workyears:			
Full-time equivalent employment......	682	685	+3
Full-time equivalent of overtime and holiday hours......................	6	6	---
Average ES salary......................	$76,447	$92,333	+$15,886
Average GM/GS grade....................	9.611	9.611	---
Average GM/GS salary...................	$34,977	$36,201	+1,224
Average salary, grades established by act of July 1, 1944 (42 U.S.C.207)...	$70,235	$72,693	+2,458
Average salary of ungraded positions...	$19,785	$20,477	+692
Personnel compensation:			
Full-time permanent..................	$17,648,000	$19,420,000	+$1,772,000
Other than full-time permanent.......	8,322,000	9,160,000	+838,000
Other personnel compensation.........	1,041,000	1,146,000	+105,000
Special personal services payments...	2,000,000	2,200,000	+200,000
Subtotal, personnel compensation...	29,011,000	31,926,000	+2,915,000
Personnel benefits.....................	5,340,000	5,879,000	+539,000
Benefits for former employees..........	52,000	54,000	+2,000

	1990 Appropriation	1991 Estimate	Increase or Decrease
Travel and transportation of persons...	1,364,000	1,432,000	+68,000
Transportation of things...............	139,000	146,000	+7,000
Rent, communications and utilities.....	1,244,000	1,299,000	+55,000
Printing and reproduction..............	340,000	352,000	+12,000
Other services:			
Project contracts....................	11,369,000	11,381,000	+12,000
Centrally furnished services.........	21,567,000	23,352,000	+1,785,000
Standard level user charge...........	1,627,000	1,681,000	+54,000
Other................................	13,040,000	12,041,000	-999,000
Supplies and materials.................	6,522,000	6,800,000	+278,000
Equipment..............................	5,328,000	5,566,000	+238,000
Grants, subsidies, and contributions...	393,453,000	410,303,000	+16,850,000
Total........................	490,396,000	512,212,000	+21,816,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Significant Items in House and Senate Appropriations Committee Reports

Item	Action taken or to be taken
1990 House Report No. 101-172	
Decade of the Brain	
1. "With the passage of the Decade of the Brain Resolution by the House and Senate, the Committee looks forward to the leadership of the Public Health Service, and its component agencies, in working with the Office of Science and Technology Policy to plan and coordinate the government-wide scientific effort to be undertaken during the 1990s." (p. 100)	1. The 1990's have been designated the Decade of the Brain. The Office of Science and Technology Policy (OSTP) is developing a plan to implement the Decade of the Brain. Representatives from NIH and ADAMHA are assisting OSTP staff in this process.
1990 Senate Report No.101-127	
Traumatic Brain Injury (TBI)	
1. "The Committee notes that traumatic brain injury is the leading killer and cause of disability in children and young adults....The Committee is aware that the interagency head injury task force representing 13 Federal agencies met in 1988 and has completed its report. This report includes recommendations for a national strategy on traumatic brain injury, emphasizing research needs in prevention, basic biology, and clinical and rehabilitation intervention. The Committee strongly urges NINDS to allocate a significant portion of the increased funding provided for additional traumatic brain injury research." (p. 125)	1. Traumatic brain injury continues to be a high priority. The NINDS recently established a new Head Injury Clinical Research Center at Boston University in Boston, Massachusetts, to study the relation between memory disorders and brain injuries. A second new center at Baylor College of Medicine in Houston, Texas, will focus on the evaluation of new treatments for physiological disturbances after head injury. NINDS intramural scientists will be working on refining methods for examining brain plasticity after stroke. If quantification proves reliable, therapeutic efforts will be directed towards promoting recovery.

Item	Action taken or to be taken
Spinal Cord Injury	
2. "The Committee is supportive of continued research on spinal cord injury which has contributed to our knowledge of the effects of growth factors on the cells and nerve fibers that make up the nervous system." (p. 125/126)	2. Research on spinal cord injury continues to shed light on potential therapies and to expand our understanding of the nervous system; however, much remains to be done to elucidate the complex and varied influences of growth factors. Recent findings suggest that nerve growth factor (NGF) does not affect all neurons in the same way. The wide range of NGF action in the central nervous system must be more clearly defined experimentally before clinical strategies that use NGF can be defined.
Adrenal grafting	
3. "It has come to the Committee's attention that support is not currently being provided for research in the area of adrenal grafting for Parkinson's disease, Huntington's disease, and Alzheimer's disease. The Committee understands that this approach may have significant benefits and urges NINDS to give consideration to supporting such endeavors." (p. 128)	3. Adrenal grafting is being studied in a major program project grant as well as in other intramural and extramural settings. Adrenal grafting has not been as successful as hoped. Reports from various laboratories around the world suggest that although adrenal implants may have some benefit, the consensus appears that it is not worth the risk. In experimental animals other approaches involving fetal implants have proven superior. NINDS is actively exploring the use of placental tissue to stimulate the regrowth of dopaminergic neurons in Parkinson's Disease.

NATIONAL INSTITUTES OF HEALTH
National Institute of Neurological Disorders and Stroke

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1990 Amount Authorized	1990 Appropriation	1991 Amount Authorized	1991 Budget Estimate
Research and Investigation..	Section 301	42§241	Indefinite	$477,380,000	Indefinite	$499,196,000
National Institute of Neurological Disorders and Stroke..................	Sections 457-459	42§285j	Indefinite		Indefinite	
National Research Service Awards......................	Section 487	42§288	Such sums as necessary 1/	13,016,000	Authorizing legislation to be requested 1/	13,016,000
Total Budget Authority......				490,396,000		512,212,000

1/ This training authority is shared with the research training programs of the Alcohol, Drug Abuse, and Mental Health Administration.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
1982	243,017,000[1/]	277,700,000	282,211,000	265,901,000[2/]
1983	274,505,000	294,361,000	297,077,000	297,064,000
1984	300,631,000	329,599,000[3/]	322,761,000[3/]	335,883,000[4/]
1985	344,601,000	379,520,000[5/]	401,403,000[6/]	395,197,000[6/]
1986	375,515,000	418,590,000	428,517,000	433,362,000[7/]
1986 Sequester				-18,635,000
1987	399,351,000	491,085,000	487,218,000	490,233,000
1988	423,193,000	554,039,000	550,172,000	534,692,000[8/]
1989[9/]	557,585,000	557,046,000	477,878,000	567,690,000
1990[10/]	493,502,000	495,203,000	498,988,000	495,625,000
1990 Sequester				-5,216,000
1991	512,212,000			

1/ Reflects the September amendment; the original request was $276,156,000.

2/ No enacted appropriation, authorized under a Continuing Resolution.

3/ Excludes $9,209,000 in NRSA training programs not considered.

4/ Includes $9,703,000 for NRSA training programs authorized under the Continuing Resolution.

5/ Excludes $13,459,000 for NRSA training programs not considered.

6/ Includes $13,153,000 for NRSA training programs.

7/ Excludes an administrative reduction of $233,000.

8/ Included funds for a reduction of $174,000 for travel and transportation costs.

9/ The House allowance excluded $14,210,000 for the unauthorized training programs (National Research Service Awards). The Senate allowance included the budget for NRSA's. It excluded $93,100,000 for establishment of the proposed new National Institute on Deafness and Other Communication Disorders (NIDCD). The appropriation included the budget for the NRSA program and provided $96,100,000 for the establishment of the proposed new institute, NIDCD.

10/ The appropriation excludes an enacted administrative reduction of $1,471,000.

Justification

National Institute of Neurological Disorders and Stroke

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
TOTAL......	665	$490,396,000	668	$512,212,000	+3	+$21,816,000
HIV/AIDS...	(40)	(16,158,000)	(40)	(17,227,000)	--	(+1,069,000)

General Statement

The National Institute of Neurological Disorders and Stroke (NINDS) supports and conducts research and research training to further the understanding of the normal and disordered function of the nervous system, (including the brain, spinal cord, and peripheral nerves), and muscles. Such disorders are numerous and varied; some are among the leading causes of death, but the majority are characterized by long-term disabilities which markedly impair the quality of life. These disorders strike all ages from the disorders of early life such as spina bifida, cerebral palsy, Tay-Sachs disease, muscular dystrophy, language dysfunction, and meningitis; through the disorders of youth and early adult life such as epilepsy, myasthenia gravis, head and spinal cord injuries, and multiple sclerosis; to the afflictions of adult life and the elderly, including stroke, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis and the dementias including Alzheimer's disease, and the prevention or treatment of disorders of the nervous system including those caused by Acquired Immune Deficiency Syndrome (AIDS).

Research and Research Training Programs

1. Biological basis research.--This program includes research on the fundamental structure and function of the brain and the nervous system; the causes and pathophysiology of dysfunctions of the nervous system; and research training in the basic neurological sciences.

2. Clinical research.--Research is directed towards the solution of clinical problems directly relevant to patients, including improved methods of disease prevention; improved methods of diagnosis; development of therapeutic interventions including drug and surgical developments and evaluations; development of neural prosthetic devices; epidemiological research, and research training in the clinical neurological sciences.

3. Intramural research.--The research efforts of this program range from fundamental studies on nerve and associated cell development, structure, and function to clinical research studies aimed at improved methods for the diagnosis, treatment, and prevention of neurological disorders. The basic

approaches involve molecular genetics, cell biology, neurochemistry, and biophysics. The clinical investigations utilize viral, immunological, epidemiological, medical and neurosurgical studies directed toward the prevention or treatment of disorders of the nervous system including those caused by Acquired Immune Deficiency Syndrome (AIDS). Research using brain imaging techniques examines the metabolic and anatomic changes in brains of patients with brain tumors, epilepsy, stroke, Alzheimer's disease, Parkinson's disease and other disorders of the nervous system.

Overall Budget Policy

The 1991 budget request for the NINDS is $512,212,000, an increase of $21,816,000 over the 1990 comparable current estimate.

The NINDS 1991 budget request for research project grants is $358,627,000, an increase of $16,843,000 over the 1990 estimate. This represents an increase of 4.9 percent. The total number of research project grants awarded in 1991 will be 1,861, a reduction of 5 grants below the 1990 level. The request will support 405 competing project grants at an average cost of $173,168, a reduction of 3.2 percent below the FY 1990 average cost. The request will support 1,456 noncompeting project grants at an average cost of $197,592, an increase of 8 percent over the FY 1990 average cost.

In FY 1991, the Institute will support 29 centers for $22,247,000, the same number and dollar level as in 1990.

Other research grants will total 267 awards for $16,413,000 in 1991, the same number as the 1990 level but with an increase of $7,000. For National Research Service Awards, an estimated 528 research trainees will be supported in FY 1991, the same as in 1990.

The research and development contract budget of $11,381,000 will support 42 contracts, an increase of $12,000 over the 1990 level.

The 1991 budget request for intramural research is $69,105,000, an increase of $4,672,000 over the 1990 level, or 7.2 percent. The request for research management and support is $21,423,000, an increase of $1,338,000 over the 1990 dollar level.

This request includes $17,227,000 for the AIDS research program. This is an increase of $1,069,000 over the 1990 level of $16,158,000 for AIDS activities.

Program Accomplishments

Extramural Research

Repetitive electrical stimulation can damage peripheral nerves. The large nerve fibers are more prone to damage than the smaller ones and the myelinated fibers more so than the unmyelinated. This damage can be prevented by periodically interrupting the stimulation or lowering the frequency of stimulation.

Microminiature electrodes placed within the brains of animals have been electrically stimulated at the levels which will be required for future neural prostheses such as visual prosthesis for the blind. A preliminary safe level has been established up to which a prosthesis could be safely operated without producing stimulation-induced damage to nerve cells. However, if these levels are exceeded, significant brain damage can occur.

An electrical circuit equivalent model of stimulating electrodes has been developed. This model will be of value in understanding the physical processes responsible for potentially harmful electrochemical reactions which can occur when electrodes are electrically pulsed in neural prostheses.

The first electrical neural recordings from the brain using microelectrodes that contain integrated electronic amplifiers was accomplished this year. Brain activity recorded with electrodes such as these may eventually be used to provide a reliable system for generating commands to control prosthetic muscle stimulators in paralyzed individuals.

A new electrode implanted through the skin with a hypodermic needle and designed for stimulation of paralyzed muscle has been investigated. The electrode uses the same basic materials as previous intramuscular electrodes but has safeguards to prevent breakage. The result is that eighty percent of these electrodes remain functional after one year of implantation compared to 35 percent of the electrodes based on the previous design.

The nervous and immune systems share specific recognition molecules for signals that originate in both systems. Neurotransmitters and their receptors, as well as immunotransmitters and their receptors, comprise a multidirectional informational exchange network through which brain and nervous system functions can be integrated with the activities of the immune and endocrine systems. Among recent developments are immune and other host-defense systems can be altered, either decreased or increased, by Pavlovian-type conditioning; such conditioning techniques have enabled some researchers to significantly prolong the life-span of mice with experimental tumors; cells of the immune system (lymphocytes, macrophage, etc.) can produce hormones and peptides that, until recently, were thought to be exclusively the products of the central nervous system; opium-like substances (enkephalins and endorphins) produced by the brain and other tissues within the body have measurable effects on immune functions; embryonic and fetal development of the nervous, immune and endocrine systems are closely linked;

and psychological stress, including depression, may significantly decrease the effectiveness of the immune system.

The gene for one of the autosomal forms of Charcot-Marie-Tooth disease has been localized to a region of chromosome 17. Additional studies will locate the gene more precisely.

New procedures to detect the presence of dystrophin, the protein product that is missing in Duchenne muscular dystrophy, have been developed. These tests have made it possible to distinguish more precisely between Duchenne and Becker muscular dystrophies as well as patients with similar symptoms that arise from a different underlying defect.

Embryonic muscle cells injected into mice with a genetic defect analogous to Duchenne muscular dystrophy have become fused with the host cells and produced dystrophin, the protein product missing in these genetically dystrophic mice. Further studies will determine the feasibility of "myoblast transfer" as a treatment for muscular dystrophy in humans.

Brain hemorrhage is a significant cause of mortality and morbidity in very low birthweight infants. In a prospective, randomized double-blind clinical trial, evidence was presented that the drug indomethacin reduced the incidence of both moderate and severe brain hemorrhage in newborns weighing less than 1600 grams.

The various stages of normal sleep are associated with changing patterns of electrical discharges located in specific areas of the brain. Preliminary work in dogs with narcolepsy have shown that there is a majority of medial medullary neurons that fire during phasic REM (rapid eye movement) and active waking movements but are inactive during cataplexy. These studies have provided interesting anatomical insights into the process of narcolepsy.

Effects of surgical therapy for epilepsy on the quality of life (neuropsychological, psychosocial, and vocational) require careful evaluation. One researcher has paid particular attention to the role of the temporal lobes in semantic memory. Damage within a specific area of the brain, Ammon's Horn area of the hippocampus, corresponds strongly to disruption of the learning of new associations. Such subtle changes in language processing may be factors affecting the quality of life after surgery.

New intensive monitoring technologies for the detection and treatment of seizures have been utilized by clinical investigators to characterize specific subclasses of epilepsy patients to guide surgical therapy and to predict long term prognosis. A retrospective study of 40 patients with seizures originating in the medial temporal lobe of the brain have been studied by scalp EEG, depth EEG, and video-taped seizures. Preliminary observations indicate that a history of febrile seizures, particularly complicated or repeated episodes, and presence of mid to anterior temporal spike/sharp wave EEG abnormalities are more important in diagnosis and prognosis than are birth difficulties or complications, frequent generalized convulsions, or a history of status epilepticus.

Aged primates have been considered as candidate models of Alzheimer disease (AD) even though one characteristic feature, the neurofibrillary tangle, had not been recognized until very recently. Last year for the first time, a 34-year-old monkey with impairment of spatial memory and habit formation was reported to have neuritic plaques and neurofibrillary tangles at autopsy. These findings support the continued study of aged primates as models for AD.

A serine protease inhibitor, alpha-ACT, has been found in the amyloid of neuritic plaques and blood vessels in both non-human primates and humans. This inhibitor of the enzymes that break down and help to turn over a number of large intracellular proteins is a possible cause of the accumulation and subsequent development of neuritic plaques and the deposit of amyloid in blood vessels in the AD brain.

The search for the Huntington disease (HD) gene is continuing. A variety of high resolution genetic and physical mapping techniques have narrowed the region for the HD gene to a small zone in the terminal end of the short arm of chromosome 4. Utilizing new markers, the presymptomatic test for HD is now estimated as 99 percent accurate when tissues from sufficient family members are available for study.

The Venezuelan pedigree of HD families continues to contribute significantly to investigations of HD. It has been observed that HD patients with onset of illness at a young age usually inherit the gene from their father. Moreover, mitochondrial genes have been eliminated as the cause of the maternal protective effect and other possible mechanisms are being studied.

This year, a major NINDS-supported clinical trial revealed that treatment with the drug deprenyl delays the progression of symptoms in patients with early Parkinson disease (PD) and postpones the need for L-DOPA therapy. Deprenyl was also found to increase significantly the time patients remained gainfully employed, a benefit that will yield increased productivity and annual savings in health care costs of hundreds of millions of dollars. Although the investigators are unsure exactly how deprenyl works, they believe that this is the first drug to actually slow the progress of a neurodegenerative disorder.

It has been established that fetal primate brain will survive implantation into an adult primate brain and grow for up to 7 1/2 months, produce dopamine, and reverse the parkinsonian effects caused by the toxin, MPTP.

Antibodies against a component of the oligodendroglial cell membrane, galactocerebroside C, cause intracellular changes that culminate in contraction and blistering of the myelin sheath. This is a newly described mechanism that may help explain how myelin is injured in multiple sclerosis (MS).

Using a pharmacological approach, it has been discovered that there exists an endogenous pain inhibitory system that comes into play, or can be activated, by electrical stimulation, by various stressors, and (or) by environmental stimuli. This system involves opiate analgesics acting on a well-characterized receptor present in brain stem and spinal cord sites that also contain endogenous opioid peptides such as beta-endorphin, methionine-enkephalin, and dynorphine. Drugs presumably relieve pain by mimicking the actions of the endogenous opioids.

Synthetic guidance channels are not merely inert, mechanical supports, but are biomaterials that actively participate in the regeneration process by influencing the cellular and metabolic aspects of the cells involved in regrowth of the nerve. Investigators have shown that diffusion of molecules into polymer tubes placed [illegible] severed nerves is essential for regeneration. Nerves that had regenerated in tubes with larger channels consisted of nerve fascicles surrounded by a loose epineurial sheath. While severed nerves placed into tubes with small channels were composed mainly of granulation tissue. It is believed that the smaller channels isolated the injured nerve from growth-promoting or trophic molecules that were present in the surrounding tissue space. This information could provide the basis for construction of novel prosthetic devices that would enhance nerve regrowth.

Work also continued on the effects of implanted fetal spinal cord on the glial scar present in injured adult cord. Some loosening of the scar tissue does appear after implantation; in unimplanted controls, a continuous lining of glial processes lined the lesion cavity. Integration of graft and host spinal cord tissue is obvious at those regions that appear devoid of scar tissue. Axons containing the transmitters serotonin, noradrenalin, and dopamine entered the graft, which demonstrated integration of host and implanted nervous tissues. These findings indicate that implantation of immature spinal tissue can reverse at least some of the anatomical damage caused by previous injury, and presents the possibility of treatment for chronic spinal cord injury.

A major advance in stroke research is the discovery that there is a period of time immediately after the stroke during which neurons surrounding the area of the lesion are sick, but still alive. This provides a therapeutic window of opportunity during which limitation of brain damage may be possible. It is known that the excitatory amino acids (such as glutamate) that are elevated in injured brain tissue mediate various effects that contribute to neuronal death. A unifying hypothesis has emerged to explain the discrepant findings that surround studies of drugs that block the actions of these molecules. Unless these antagonists are given locally in very high concentrations, they ameliorate brain damage only when there is some remaining energy supply for the neuronal tissue. This information may be important in delineating a mechanism for limiting the extent of damage to brain tissue after a stroke.

The hypothesis that glutamate antagonists would be systematically effective in protecting cortical cell cultures against hypoxic injury was strengthened by a study to test a series of phencyclidine ligands for their neuroprotective action. The tested ligands were able to protect cortical cells against injury from either externally administered glutamate-type drugs, or hypoxia, with nearly identical potency and efficacy. This work is important because it provides a model system that mimics the sequence of events in humans after cerebral ischemia, and, therefore, provides a realistic model in which to test new pharmacological agents to combat the effects of ischemia.

Using newly developed techniques of magnetic resonance (MR) spectroscopy, clinical investigators have studied 223 stroke patients within hours and days of the onset of stroke. By studying the acidity of the stroke-injured brain, researchers think they may have discovered a method for determining what part of the brain has been irreversibly injured by stroke. Changes in the size of the brain injury as time passes have been observed. Therefore, a better estimate can be made of how soon ischemic stroke must be treated.

Trends in stroke incidence, prevalence, and one year case-fatality rate in three decades from 1953 to 1983 have been studied. The case fatality rates in men declined dramatically from 34% to 14% during this period. The incidence of stroke rose in men from 5.7% to 7.9% over three decades; there was no change in incidence for women. Prevalence of stroke also increased. It is the investigator's speculation that these increases in incidence and prevalence occurred as a result of changes in diagnostic criteria, a lessening of stroke severity, or improved care of stroke patients. The increases in incidence and prevalence occurred despite a decline in the prevalence of hypertension.

A recent report from an ongoing study states that U.S. Blacks have a statistically significant higher, age-adjusted rate of stroke than Whites. There were no differences in the severity of the strokes between the two populations. Those Blacks who had strokes were compared with Whites and found to have a higher incidence of high blood pressure, heart attack, and diabetes. This result emphasizes the importance of treating risk factors in Blacks in order to reduce stroke incidence.

Investigators have completed a pilot safety study of tissue plasminogen activator (TPA) to treat ischemic stroke. The study required early treatment within 90 minutes of the start of the stroke. Since TPA dissolves blood clots plugging arteries, early reperfusion was sought before irreversible brain injury occurred. Although brain hemorrhages are a risk of this treatment, the overall impression was that TPA may offer partial improvement for some patients if given soon enough after the stroke begins.

For a particular class of brain tumors in children, it is now known that iron is important for the survival of the tumor cells and that depletion of iron by an iron-binding compound (deferoxamine) will kill the cells. A group of researchers are now collaborating in a study of the anti-tumor effects of a newly developed class of compounds that consist of complex polymers coupled to deferoxamine. At least one combination studied so far is not toxic to cultures of normal cell lines. Consequently, more than a ten-fold dose of the deferoxamine can be given safely in that combination. These studies could well lead to clinical trials in children with progressive neuroblastoma that does not respond to conventional therapy.

Significant progress was made in defining the responses of a specific type of adrenal tissue and isolated cells from that type of adrenal tissue after implantation into the central nervous system. Specifically, such implants appear to be able to reduce pain sensitivity in a chronic pain model. Chronic-pain rats with adrenal tissue implants, but not control implants, do not exhibit the retardation in weight gain normally seen in the chronic-pain rats. Furthermore, pain-specific responses are reduced in the chronic-pain model with adrenal implants, but not in control animals. This reduction in specific responses can be blocked by the opiate antagonist naloxone. These results are very encouraging, because they suggest that certain adrenal tissue implants may be of value in the alleviation of chronic pain.

In a fundamental chemistry study, researchers developed methods to synthesize high-specific-activity fluorine-labeled radiotracers that will expand the clinical usefulness of PET. Using this new synthetic strategy, radiotracers are being developed for studies of neural function in dopaminergic motor systems and for PET studies of substance abuse. This represents a major advance in the development and streamlining of the chemistry and related technology necessary for PET to be applied to a broader spectrum of problems in biology and medicine.

Research Training and Career Development

The Institute continues to promote and sponsor research training in neurological processes in order to address the needs and opportunities present. These programs develop a cadre of skilled investigators capable of applying the research tools of modern biology to the investigation of neuronal mechanisms. Emphasis has been given to training in the basic neurosciences including molecular biology, cognitive science, developmental neurology, neurobiology, neurochemistry, neuroimmunology, neuropharmacology, neurosensory physiology and biophysics, and neurovirology.

The NINDS gives special emphasis to the recruitment and research training of clinical investigators in the neurological and neuromuscular sciences. The program supports training for research careers aimed at the development and evaluation of improved methods of diagnosis, prevention, therapy and the application of experimental animal research to clinical problems of the human nervous system. Major clinical areas of research training include: cerebrovascular disorders (including stroke), medical neurology, neuromuscular disorders, neurosurgery, neuroepidemiology and neuropathology.

Career development in the broad spectrum of the areas of research responsibility of the NINDS has been supported through the Research Career Program which includes Research Career Development Awards (RCDA), and Clinical Investigator Development Awards (CIDA). Former awardees continue to be at the forefront of research on improved diagnostic methodologies, etiology, treatment, and prevention of disorders of the nervous system, the neuromuscular apparatus, as well as pain. The majority of awardees compete successfully as principal investigators on NIH-funded research grants soon after completion of their research career program. The breadth and depth of their research activities, volume of publications, and advancement in academic positions point toward attainment of Research Career Program goals. In particular, the CIDA has provided a highly effective method for the recruitment and preparation of future clinical investigators in the neurological disorders and stroke.

Intramural Research

Using recombinant DNA technology, the genes for human beta-adrenergic, five types of muscarinic cholinergic receptors and two dopamine - D_2 - receptors have been cloned, sequenced, and expressed in mouse cells in tissue culture. The dopamine D-1 receptor has been purified over 8000-fold from rat striatum and will be used to obtain amino acid sequences need for cloning of the gene for this receptor. Expression of these receptors in tissue culture cell lines has the potential to dramatically change the use of animals in receptor research. Changes in the receptor molecules have been induced to determine the structures essential for biological function. Cloning of the human receptor cDNAs has permitted mapping of the distribution of the mRNAs encoding the receptor proteins in both human and rat brain; a particularly interesting finding is that the m5 receptor is the only muscarinic acetylcholine receptor subtype expressed by dopamine neurons. These studies suggest the possibility of developing drugs targeted to subtypes of neurons.

Research on neurofibromatosis, a genetic disease which results in tumor formation, may be facilitated by discovery of a new pathognomonic ophthalmologic sign which has permitted pre-symptomatic detection of NF2. New guidelines have been proposed for surgical intervention of the acoustic neuromas in NF2.

Lysosomal storage diseases are caused by genetically determined enzyme deficits. Over the years several such deficits have been defined and replacement therapy envisioned. Gaucher patients in the enzyme replacement efficacy trial have had clearly demonstrable clinical benefit. Their anemia has been corrected; the size of the enlarged spleens and livers has decreased; and there are indications of skeletal improvement by magnetic resonance imaging. In addition, they all state that they feel much better; many have been able to return to work; and they all emphatically state that the quality of their lives is greatly improved.

The abnormality of intracellular cholesterol processing previously discovered in our laboratories has been successfully applied for diagnosis, carrier detection, and prenatal monitoring of pregnancies at risk for Type C Niemann-Pick disease. Knowledge of the abnormal storage of free cholesterol has led to strategies to alter cholesterol availability and uptake in tissues of patients in a therapeutic trial. An animal model of this disease has been developed.

Recently our laboratories have isolated, characterized and chromosomally localized the cDNA for amyloid β-protein which forms most of the amyloid deposited as plaques and in neurofibrillary tangles of and around vessel walls (amyloid angiopathy) in the aging brain. Modulation of this gene's expression has been achieved, in both vascular endothelial cells and neurons, with growth factors and interleukin-1 in tissue cultures. These studies could lead to control of amyloid precursor production as a prophylactic approach in Alzheimer's and senile dementia.

In snails (Hermissenda) conditioning-specific changes in four phosphoproteins were observed 24 hours after conditioning. One of these proteins, cp 20, was purified to apparent homogeneity and found to be a guanosine triphosphate (GTP)-binding protein. When injected back in the animal's neurons, cp 20 changed specific membrane channels in a manner indistinguishable from changes caused by conditioning suggesting that this protein may play a central role in memory acquisition or retention.

Preliminary studies indicated that prevention or reduction of the post-ischemic hypoperfusion also may significantly ameliorate the outcome of ischemic brain damage, and these findings may be relevant to the possible treatment of the transitory cerebral ischemia.

The amino acid glutamate is a major excitatory neurotransmitter. Specific receptor proteins have been isolated and used for the production of an antiserum, containing polyclonal antibodies. The gene for this receptor has been isolated and is being characterized.

A subtype (T-type) Ca^{2+} channels in thalamic neurons mediate the shift from tonic to burst firing. This is the first demonstration of a specific electrophysiological function of an identified Ca^{2+} channel type.

A peptide sequence (Ser-Ala-Ala-Ser-Leu-Asn) that is present in coat proteins from several neurotropic viruses (polio virus, herpes simplex virus, HIV) can activate an entirely novel ligand-gated cation channel in cultured hippocampal neurons. This channel is permeable to $Ca2+$ ions and may account for the neurotoxicity of these viruses or the receptor for the peptide sequence could serve as attachment sites for the viruses.

The embryonic origins of the LHRH neurons in the hypothalamus have been determined to be in the olfactory placode, with subsequent migration of these neurons during prenatal life, along extra-CNS nasal tracks and then into the brain proper where they assume their adult distributions and circuits. An in vitro organotypic culture model of these cells in nasal areas, as well as brain, for regulation of gene expression and migration studies has been developed.

Distribution of the myelin-specific proteins (MAG, CNP, and MBP and their mRNA precursors) in actively myelinating oligodendrocytes demonstrate distinct mechanisms of transport, translation and assembly for the proteins targeted to the myelin sheath and show how the essential components of myelin are assembled.

Gangliosides were shown to have profound effects on the modulation of protein phosphorylation in CNS myelin and in skeletal muscle, suggesting that they can serve as multifunctional biomodulators.

An immunocytochemical survey of central nervous system tissue using well characterized antibodies and antisera has uncovered herpes virus type - related antigen in glial cells located in demyelinative lesions from 3 out of 31 MS cases and one case of brainstem encephalitis. The data show that herpes viruses produce a broader spectrum of neurological diseases than has been suspected previously, and suggests a possible link between herpes viruses or related agents and human demyelinative disease.

MRI scanning using gadolinium to assess blood brain barrier (BBB) function, showed that patients with early MS frequently show rapidly (monthly) changing foci of BBB abnormalities which are not associated with clinical symptoms. This indicates that in MS there is a disorder of BBB function and that the brain lesions may not be faithfully represented by functional abnormalities.

In mice, it has been demonstrated that T-cell lines that recognize the encephalitogenic peptide of myelin basic protein can lyse brain capillary endothelial cells that have been cultured with the encephalitogenic peptide and gamma interferon to induce class II MHC molecules. Occurrence of this phenomenon in vivo would provide a mechanism for breakdown of the blood-brain barrier by cytotoxic T lymphocytes.

Regenerating and denervated muscle fibers in the human muscles biopsies express HNK-I antigen. HNK-I appears to be an adhesion molecule that appears only during certain stages of human muscle development and maturation. This antigen is also present in the satellite muscle cells and could play a role in muscle regeneration.

In spite of the absent dystrophin, the muscle fibers in Duchenne's muscular dystrophy generate normal force. This indicates that the muscle weakness in Duchenne's dystrophy is not due to an intrinsic defect in the contractility of muscle fibers but rather due to actual loss of muscle fibers.

High levels of antibodies to complex glycolipids have been detected in the sera of some patients with Guillain-Barre syndrome and other forms of peripheral neuropathy. Injections of some of these antibodies into the nerve of appropriate experimental animals causes demyelination suggesting that the antibodies play a causal role in human disease.

The laboratory diagnosis of a viral (JC virus) induced demyelinating disease in humans, progressive multifocal leukoencephalopathy, has been firmly established by utilizing *in situ* DNA hybridization technology for either biopsy or autopsy tissues. The application of such molecular biological techniques has led to the understanding of the pathogenesis of this central nervous system (CNS) disease because it has allowed the identification of JC virus infection of B-cells. In the absence of T-cell control and immunosuppression as occurs in AIDS, a subunit of these B-cells enter the brain to spread infection to the myelin-producing oligodendrocytes. In the B-cells on myelin-producing oligodendrocytes, viral replication may be controlled at a molecular level by a transactivity factor recognizing a specific sequence of the HIV genome. This discovery resolves a very difficult biological problem of determining how a common virus infection can enter the CNS and cause a fatal, multifocal demyelination.

Three new hantavirus serotypes, latent in wild American rodents from Alaska to Florida have been defined. These are now important serotypes in worldwide study of these viruses, the cause of major plagues of hemorrhagic fever with renal syndrome (HFRS) over much of the Eurasian landmass. HFRS was a major cause of death in U.S. troops in Korea and today is one of the most important endemic virus diseases in China and the USSR.

Unconventional viruses causing presenile dementias in man have been elucidated as replicating infectious polypeptides or infectious amyloid monomers, generated spontaneously from normal host precursor proteins. There is a million-fold increased likelihood of spontaneous *de novo* generation of such a new pathogen when certain familial point mutations occur in the precursor gene. This is a new paradigm in virology. Since infectious polypeptides are enormously resistant to inactivity and can cause serious iatrogenic epidemics, such as the thousands of scrapie cases in sheep from contaminated louping-ill vaccine in England in the 1940s, the recent CJD deaths (fortunately only a dozen) from CJD-contaminated growth hormone, and the current epidemic of bovine spongiform encephalopathy (BSE) in the United Kingdom from scrapie contaminated bone meal fed to dairy cattle; we cannot discount these agents only as rare causes of human dementia. We have developed methods to inactivate these resistant infectious agents in surgery, autopsy rooms and laboratories.

In Parkinson's disease partial dopamine agonists may confer therapeutic benefit by occupying all dopamine receptors, but act only weakly to stimulate them, thus providing optimal levels of dopamine receptor excitation, but preclude their hyperstimulation. A clinical trial to evaluate the practical value of this possibility showed that the partial dopamine agonist, terguride, improved the therapeutic index of levodopa in patients with Parkinson's disease. As a result, levodopa in doses sufficient to ameliorate parkinsonian symptoms, no longer induced abnormal involuntary movements.

A hemiparkinsonian model of human Parkinson's disease was developed in monkeys. This model of Parkinson's disease, which is produced by treatment with MPTP, has been treated successfully with brain grafts from the monkey fetal brain. In several animals the recovery after grafting was nearly complete. Investigation of the mechanism of the recovery suggests that it may be related to sprouting of adult neurons in the host brain that is stimulated by the grafts. Adrenal and fetal tissue allografts were demonstrated to induce partial functional recovery in animals with parkinsonism. Immunohistological assessment demonstrated functional survival of the fetal grafts and prominent sprouting of dopaminergic fibers from residual neurons in the host brain surrounding the area of implantation. Surgical cavities alone are just as successful as adrenal implants in reducing Parkinson's syndrome in monkeys, but fetal tissue is superior. Recently it was found that cells of the fetal placenta implanted in parkinsonian monkeys will reverse the syndrome as effectively as fetal tissue. The placenta may be an alternative use of fetal tissue to stimulate regeneration of damaged dopaminergic neurons in Parkinson's disease.

Using magnetic stimulation, it is possible to determine in humans which areas of the motor cortex are responsible for contraction of particular muscles. This method was used to show for the first time plastic reorganization by enlargement of the mapped cortical representation areas targeting muscles immediately proximal to the stump after amputations and to the lesion level after spinal cord injury.

An immunotoxin consisting of antitranserin receptor antibody conjugated to recombinant ricin A chain has been developed to target the toxin (ricin A) to destroy tumor cells. Intrathecal administration of this immunotoxin will be tried as a means of treating patients with heptomeningeal spread of their primary tumors causing corcinormatous meningitis which is otherwise untreatable.

The outcome of severe head injury, as evidenced in the Traumatic Coma Data Bank, was shown to relate to postresuscitative GCS score, intracranial pressure (ICP), and other factors. Age at time of injury has been shown to be a significant independent predictor of outcome. It is likely that the age effect on outcome following head injury is dependent upon an alteration in the pathophysiologic response of the aging central nervous system to severe trauma, and not an increased incidence of non-neurological complications or other clinical parameters. A new classification of head injury has been introduced, based primarily on computerized tomography, which offers significant advantages over previous methodologies for the prediction of both outcome and elevated ICP.

A comprehensive monograph has been completed on the etiology, incidence and prevalence of neurologic diseases, including cerebrovascular diseases, Alzheimer's disease, epilepsy and peripheral neuropathies. The monograph also includes an overview of the methods of neuroepidemiology.

AIDS Research Program

NINDS AIDS Program

Neurological symptoms are recognized in about half of patients with AIDS, many of whom develop the devastating AIDS dementia complex. Post-mortem studies reveal that as many as 80% of AIDS victims may have neurological involvment. The responsible virus, HIV-1, seems to have a predilectation for the cells of the nervous system, and may seek these cells as a harboring place, causing latent infection.

Building upon the strong foundation of knowledge we have achieved through basic molecular research of neural cells as well as retroviruses related to HIV, we are attempting to understand the relationship between the virus and the human nervous system. Active research is now in progress to determine how the virus enters the brain through the usually impenetrable "blood-brain barrier" and how it damages nerve cells. Understanding these phenomena will allow researchers to prevent or ameliorate the neurological symptoms associated with AIDS.

Recent Research Accomplishments

Extramural Research

The mechanism by which the human immunodeficiency virus (HIV) injures the nervous system is unknown. Recent studies suggest that damage occurs either by direct viral infection of brain cells causing alterations in the metabolism of the affected elements, or indirectly by the toxic action of viral or cellular products. Early in the AIDS epidemic it was believed that opportunistic infections caused most of the recognized cases of neurological dysfunction in AIDS patients. It is now well established that these account for some 30% of the neurological complications while the rest seem to be direct effects of the virus and involved inflammatory cells on nervous tissue. HIV has been isolated from cerebrospinal fluid, brain tissue, spinal cord, and peripheral nerve, and HIV genetic material has been identified in nervous tissues by hybridization, electron microscopy, and other sophisticated laboratory techniques in patients with neuro-AIDS.

The monocyte/macrophage, a type of blood cell, performs important defensive functions against agents perceived as foreign to the body. In HIV infection, unfortunately, these cells are the reservoir for the virus which they carry to various organs, including the brain. These cells have been implicated in the pathogenesis of neuro-AIDS, and are the cells in the brain that harbor HIV. One of the products secreted by macrophages is tumor necrosis factor (TNF) that mediates both beneficial and toxic events. Elevated serum levels of TNF were found in HIV-infected children with progressive encephalopathy more often than in AIDS patients having no neurological involvement. The progressive encephalopathy is characterized by loss of developmental milestones in infants and by progressive dementia in responsible for the multinucleated syncytial cell formation seen in the AIDS brain. In the fetal brain, it appears that the astrocyte population develops a persistent infection with little cytopathology evident. Analysis of this neurotropism is continuing using brain derived cultures and both lymphocyte and macrophage derived isolates of HIV-1. New recombinant pseudotypes of HIV-1 are also being investigated for their cellular interactions, particularly at the membrane level.

Clinical and immunological studies of patients with HTLV-1 associated spastic paraparesis, polymyositis, and encephalomyeloneuropathy have drawn a direct link between this virus and the progression of neurological disease. Cellular immune response to HTLV-1 proteins has been identified as recognizing regions of the viral envelope protein. There also seems to be a cooperative effect of HIV-1 and HTLV-1 coinfection in certain T-cells demonstrated in culture experiments.

In an investigation of clinical immunological and virological aspects of tropical spastic paraparesis (TSP) with patients from the Caribbean and South America in the Clinical Center, 50-percent had MRI lesions which indicated that the disease was not confined to the spinal cord. Development of new techniques for cell culture have enabled the isolation of a retrovirus from 12 cell lines derived from the blood and CSF of six patients. Most recently the virus has been isolated from a seventh patient (the first American caucasian studied) and his Japanese wife (who is asymptomatic). Initial findings indicated biological differences between viruses and classical HTLV-I. Antibodies to HTLV I have been found in 30% of a group of normal Jamaicans with indices of abnormal T cell activation (IL-2 and Class II MHC) and spontaneous proliferation in culture. Molecular characterization of the virus isolated was initiated. The approaches which had enabled isolation of retroviruses from six TSP patients are being applied to the study of multiple sclerosis.

A number of immunological abnormalities, such as impaired T-CD4 lymphocyte function (capacity to differentiate into effectors which mediate delayed hypersensitivity and cytotoxicity) have been discovered in patients infected with HTLV-1.

In addition to TSP, data have been obtained which suggests a putative etiological role for HTLV-1 in polymyositis, neurofibromatosis and achnoiditis, and possible involvement of this virus in some forms of primary lateral sclerosis.

Approximately 20 different T-cell lines derived from blood or CSF of patients with myelopathy express HTLV-I. Biological differences e.g., growth conditions, T-cell responses, etc.) between these viruses and conventional HTLV-1 have been identified. Of considerable interest has been the detection by PCR of HTLV-1 gene parts in patients with chronic neurological diseases, (not MS) who lack antibodies against this virus.

Research Plans

Extramural Research

Research suggests that brain HIV isolates constitute a distinct serologic subgroup with shared biologic characteristics that are different from non-central nervous system isolates. Recombinant viruses composed of genetic material from two different AIDS viruses will be studied to identify gene(s) that control kinetics, viral replication, and neurotropism.

HIV 1, is implicated in the etiology of neuro-AIDS. It has been generally accepted that a CD4 receptor must be present on a cell surface for the AIDS virus to attach to and penetrate the cell. This receptor is instrumental in the infection of lymphocytes and has been suspected to play a role in infection of brain cells. Recent studies using cells derived from human fetal dorsal root ganglia and two different human brain tumors grown in tissue culture indicate that these cells can be infected even though they lack a CD4 receptor. Further research will pursue this lead.

The drug AZT significantly decreases mortality and frequency of opportunistic infections in AIDS patients, and delays the development of AIDS in presymptomatic individuals. A high drug level in the blood helps maintain a therapeutic drug level in the central nervous system. Recently, it has been reported that the co-administration of probenecid will delay AZT elimination resulting in higher blood levels. How to modify the transport and distribution of drugs like AZT to be even more effective in the treatment of neuro-AIDS will be investigated.

The concentration of quinolinic acid (QA), a metabolite of L-tryptophan, that is found in the cerebrospinal fluid, is increased in HIV-infected individuals, especially those with neuro-AIDS. The concentration of QA correlates with the severity of AIDS dementia complex. The level of QA falls with AZT treatment which in turn is followed by improved neurological function. Further studies on the role of QA in diagnosis and its action in the pathogenesis of AIDS dementia will be done.

Intramural Research

The use of non-human primates, particularly rhesus and African green monkeys, will investigate the SIV_{sm} neurologic disease that resembles HIV-1 brain infection. In addition to histopathologic descriptions, studies will include the importance of biochemical markers, eg. quinolinic acid release, in the mechanism of brain damage.

Chimpanzees inoculated with several strains of HIV-1 will be monitored for viral isolations and antibody specificity to virion components related to strain variations.

Functional analysis of individual HIV-1 gene products in determining effects on the immune and nervous system will be conducted using transgenic mouse models.

A significant committment to a longitudinal study in collaboration with the Bethesda Naval Hospital has been established to conduct extensive tests on the clinical, immunological, virological, and neuropsychological status of AIDS of newly seroconverted patients. Effects of HIV-1 infection on both the central and peripheral nervous system will be documented in this inter-agency program.

Further documentation of HIV-1 related neuromuscular disorders and their differentiation from AZT induced myopathies will include the role of macrophages and T-cell infiltration examined by muscle biopsy. Alteration of clinical use of AZT may be considered.

Molecular identification of HIV-1 in specific cell types of the nervous system will be coordinated with similar identification of opportunistic infections common to AIDS. Use of clinical samples from demyelinating brain tissue and extraneural sites of infection will be more extensively studied.

The mechanism of HIV-1 induced AIDS dementia complex or encephalopathy has implicated both neurons and macroglial cells in pathogenesis. Results on neural derived cells in culture will be expanded to include microglial cells in order to test the effect of HIV-1 infection in potential target cells in the human brain.

Identification of both intra- and extra-cellular factors including cytokines that promote the neurotropism of HIV-1 will be made. This will also involve the molecular characterization of neurotropic strains isolated from neural tissues of AIDS patients as well as the construction of recombinant HIV-1 pseudotype viruses.

Studies will focus on the potential therapeutic effects of an inactivated HIV-1 vaccine which lacks the viral envelope proteins. Challenge of chimpanzees with this inoculum will include investigation of strain variations for protection against infection and the nature of a long-term protective immune response.

Clinical and epidemiological studies will assess the pattern of HTLV-1 infection associated with neurological diseases. Patients from Jamaica and South America will form the largest group to be studied. Viral isolations, cell mediated immune response to specific virion components, and molecular hybridization will be done on clinically derived specimens.

Examination of T Cell markers associated with tropical spastic paraparesis and HTLV-1 infection will focus on the presence of IL-2 receptors and DR molecules. The identification of specific CTL response in HTLV-1 infection will be followed. Also the role of HTLV-1 in other neurologically related disorders, e. g., multiple sclerosis, will be examined.

The relationship between HIV-1 and HTLV-1 infections will be studied both at the neurobiological and molecular levels. Target cells for these viruses may be similar. Experiments to test whether viral non-structural regulatory proteins which act together to enhance infection are significant factors in the pathogenesis of disease.

National Institute of Neurological Disorders and Stroke

Biological Basis Research

Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$261,614,000	$273,354,000	+11,740,000

Purpose and Method of Operation

Biological Basis research is primarily responsible for stimulating and supporting research to provide new information on the structure and function of the neurological systems as a basis for development of methods for disease prevention. The underlying causes of most neurological disorders are not known at the present time. More and more, multidisciplinary approaches to basic problems are proving to be productive. Communication among investigators and technology transfer are fostered by selective support of research workshops, symposia and conferences.

Studies of fundamental mechanisms in the nervous system not only provide the key to prevention, but in addition, develop the research techniques and methodologies that are adapted by clinical investigators. Research physicians are often trained in basic laboratories which provide the rationale and methods for studying the pathological process. Support is provided through research grants, Research Career Program awards, research and development contracts, and National Research Service Awards.

The Institute's research training budget supports Individual National Research Service Awards (NRSA) which are exclusively postdoctoral, and Institutional NRSAs which emphasize postdoctoral research training, but also provide support for a limited number of predoctoral trainees in selected research disciplines of national shortage.

Through the Research Career Program, specifically the Research Career Development Award (RCDA), the Institute promotes and supports career development of neurological scientists. Awards provide salary support to enhance the research capability of individuals who, in the formative stages of their careers, have demonstrated outstanding potential for contributing as independent investigators to health-related research in the basic sciences.

Rationale for the Budget Request

The 1991 request is $273,354,000, an increase of $11,740,000 above the 1990 appropriation. The following are the program plans for 1991:

Extramural Research

Methods of safely stimulating peripheral nerves at high stimulus levels will be developed.

Electrodes for microstimulation of the central nervous system for use in neural prostheses will be perfected.

A direct interface with specific central nervous system neurons will be investigated by means of cultured neurons grown on an electrode probe and inserted into the central nervous system.

Experimental touch, force, and finger angle transducers will be evaluated on the hands of quadriplegic individuals. The transducers should provide the individuals with sensory feedback and improve control of their functional neuromuscular stimulation systems.

Studies to improve functional neuromuscular stimulation in quadriplegic individuals by providing control of the wrist and the triceps muscle in the upper arm will begin.

Studies to improve the lifetime of electrodes used for functional neuromuscular stimulation and studies to provide better methods of placement of these electrodes in paralyzed individuals will begin.

Future investigations will include more detailed research on the basic mechanisms involved in neuroimmunomodulation. The pathways connecting the nervous system with the organs and tissues of the immune system will be studied such as the innervation of the thymus, spleen, bone marrow, lymph nodes, etc. The various receptors in the nervous system for immune "messengers" such as cytokines and leucotrines will be localized and investigated. The different "feedback" controlling mechanisms must be uncovered. The limits of conditioning on immune function will be established.

The utilization of event-related potentials in a variety of studies is anticipated.

The areas of the brain that produce these electrical waves are not known, and will be sought out. Experiments involving event-related potentials will probe information handling by the brain with the aim of understanding the dynamics of certain mental processes. The presence, absence, or changes in these potentials will be studied in a variety of neuropathological conditions such as brain injury, stroke, and developmental abnormalities.

The genetic locus for the juvenile form of Batten's disease has been mapped to the long arm of chromosone 16 using linkage analysis. Work to understand the molecular pathology of Batten's disease may provide new strategies for prevention and treatment of this disorder, as well as insights into basic cellular functions, such as processing of organelle membranes and accumulation of pigments during aging.

Neuroscientists in recent years have focused on understanding the role of growth factors in preventing the atrophy and death of nerves after injury. One group of neuroscientists has developed a procedure through which specific growth factors may be identified and ultimately isolated. Application of this procedure could lead to the discovery of molecules that will promote repair processes after damage to specific areas of the brain.

Detailed molecular biological studies have characterized five components of the acetylcholine receptor molecule at the neuromuscular junction in human tissue and several animal models. The mechanisms by which the components are assembled and the role of other proteins are being investigated. These basic studies of an easily accessible model receptor system are expected to provide clues to the synaptic transmission between nerve cells in the brain.

The observation of chromosomal translocations has greatly aided the study of neurofibromatosis 1 (NF1) in the past two years, and the localization of the gene for this disorder has been narrowed to 0.01% of the human genome. Investigators are optimistic that they are closing in on the NF1 gene, with the result that important light may be shed on the nature of the disorder, the mechanism of tumor formation, and the developmental biology of the neural crest. Other studies on neurofibromatosis 2 (NF2) have localized the gene for this disorder to chromosome 22. Studies indicate that this gene may be a 'tumor suppressor' gene, similar to that found for retinoblastoma. Efforts are continuing to map the location of the NF2 gene more precisely.

Most technologies for transferring genes into cells require that the cells be able to divide. Scientists now have developed a new technique which uses a viral vector for introducing genes into non-dividing cells--such as neurons--and obtaining expression of those genes. This technology should greatly facilitate the study of neuronal development, differentiation and function, and possible approaches for altering gene defects in neuronal diseases.

Many patients who had polio 20-30 years ago are experiencing new symptoms of pain and muscle weakness apparently related to the original illness. The hypothesis that the new symptoms are the result of chronic muscle overuse that precipitates a loss of motor neurons will be tested by developing an animal model in which the effects of partial muscle denervation can be observed.

Neurotransmitters and neuromodulators are believed to play a crucial role in the genesis of seizures. An NINDS researcher has developed a method of including microdialysis in intracranial depth electrodes. This new technique will allow for measurement of neurotransmitters, neuromodulators, and antiepileptic drug levels during seizure interictal and ictal periods. This ability to measure dynamic chemical events as well as trace quantities of these substances will provide opportunity to correlate these changes with electrical seizure activity.

Kindling is a chronic animal model of experimental epilepsy in which some part of the brain's limbic system receives electrically repetitiuous stimulation at an intensity initially subthreshold for convulsions. The stimuli induces a progressive increase in excitability leading to epileptogenesis which once established, persists even after cessation of the electrical stimulation. Investigators are exploring why neurons become prone to epileptiform discharges and what cellular and synaptic events are responsible for maintenance of the epileptiform state.

Further development of recombinant DNA techniques will be supported to facilitate the identification of genetic markers for Alzheimers disease (AD). Molecular genetic studies will be expanded to further refine knowledge of the amyloid plaque and its gene, as related to AD.

Monoclonal antibody techniques will be used to study differences between normal and AD brain cells with repect to: neurotransmitters, receptors, and metabolic regulatory molecules; intracellular structural and transport proteins; and molecular genetic processes.

Studies on the molecular basis of the selective vulnerability of the brain in general and of specific neurons and other brain cells in particular, will be done to provide new approaches to therapy and (or) prevention of many degenerative brain disorders of late life such as Parkinson and Alzheimer diseases.

Studies to determine the mechanism by which the naturally occurring neurotoxin, quinolinic acid (QA), causes brain cell destruction and produces HD-like symptoms in rodents will continue. Drugs that block the destructive effects of QA will be tested in tissue culture and in rats.

Basic studies on neural tissue growth and regeneration after implantation into a host brain and the effect of growth factors on regeneration and repair will be encouraged. Dopamine producing cell grafts in particular will be studied in an effort to prolong their survival.

Research on the molecular basis of infection of the nervous system, neurotropism of infectious agents, immunological phenomena associated with viral infection, and genetics of virus and host resistance and latency will be pursued.

Since nerve growth factor (NGF) is available from commercial and laboratory sources in relatively large amounts, its use to treat head or spinal cord injury has been proposed. It was shown that, after a lesion of the forebrain, receptors for the factor are lost on the side of axotomy; in animals treated with NGF, the receptor density remains at least equal to that of uninjured brains. Experiments are planned to further test the effects of NGF and other growth factors on glial cells in order to identify the cellular basis for regeneration. In addition, other growth factors derived from nervous tissue, muscle, and connective tissue have been identified that affect neuronal survival and regeneration. Several studies are planned to use evaluate these factors after injury to the nervous system.

One of the most exciting new areas of potential treatment for central nervous system (CNS) trauma is the use of nervous tissue from fetal animals to replace damaged areas of the adult brain or spinal cord. Much work needs to be done to understand the interactions of the host nervous system and the implanted tissue, to demonstrate the long-term survival and growth of the implants, and to critically assess the potential of the grafts to restore lost function. It has been shown that normal numbers of cortical neurons and glial survive after transplantation into injury sites in motor cortex, that connections are made between the host brain and the transplants, and that animal motor behavior is affected by the transplant. Fetal cortical grafts ameliorate the atrophy that occurs in the brain after cortical injuries, and removal of the transplant results in a significant deterioration in motor performance. Likewise, in injured spinal cord, implants of fetal tissue fill the cavities formed by the degenerative processes. Studies have now begun of the behavioral and functional recovery possible after spinal cord injury and implantation.

Reduced blood supply to the brain, such as occurs in stroke, can result in selective loss of certain populations of neurons. The delayed loss of vulnerable neurons is associated with increased neuronal activity before cell death. It has been shown that the efficacy of one of the most potent inhibitors of these neurons, adenosine, is attenuated during critical, early post-ischemic periods. This reduced level of adenosine inhibition contributes to increased neuronal activity and may therefore contribute to neuronal death. A clear understanding of the cellular mechanisms that destabilize selectively vulnerable neurons could ultimately aid in our ability to treat and prevent the often catastrophic effects of transients ischemic events.

From a continuing series of experiments on brain resuscitation after cardiac arrest, two particularly important accomplishments show promise. First, minimal hypothermia (cooling of the brain) extends the time that the heart can be arrested, then resuscitated with good cerebral outcome, to about 15 minutes. Second, a reproducible model of severe arrest has been established that uses standard post-arrest therapy with accurately controlled normothermia. Mild hypothermia (34°C) induced after the onset of ventricular fibrillation, with head cooling during ventricular fibrillation and reperfusion cooling by cardiopulmonary bypass for one hour after arrest, lessens the amount of brain damage. Attempts to translate this observation to the clinical situation have been immediate. Studies are now being designed to test the effect of hypothermia on cerebral outcome after resuscitation of victims of cardiac arrest. This promising accomplishment also provides an interesting example of the importance to clinical science of basic research in an animal model.

2. Research Training and Career Development

The Institute will continue to encourage and support research training on the fundamental structure and function of the brain and nervous system and the causes and pathophysiology of dysfunction in the nervous system. Particular emphasis will be placed on studies of neurosensory mechanisms of pain; training in basic science areas related to head and spinal cord injury, including neural regeneration and prosthetic research and to neurogenetic disorders.

Through the Research Career Program, the Institute will promote and support the development of promising young scientists in the following areas: cerebrovascular disorders, developmental neurology, neurobiology, neurochemistry, neuroimmunology, neuropharmacology, neuroradiobiology, neurovirology, neural regeneration and plasticity, neurosensory physiology and biophysics.

National Institute of Neurological Disorders and Stroke

Biological Basis Research

	1990 Appropriation	1991 Estimate	Increase or Decrease
Impact Data			
Neurological disorders of early life	$38,785,000	$40,400,000	+$1,615,000
Neurological disorders of adult life	14,005,000	14,589,000	+584,000
Stroke	14,324,000	14,921,000	+597,000
Epilepsy	15,404,000	16,046,000	+642,000
Demyelinating disorders	12,467,000	12,986,000	+519,000
Neuromuscular disorders	16,440,000	17,125,000	+685,000
Infectious diseases of the central nervous system	9,120,000	9,500,000	+380,000
Trauma and injury	28,462,000	29,648,000	+1,186,000
Tumors	2,456,000	2,558,000	+102,000
Disorders due to neurotoxicants	3,068,000	3,195,000	+127,000
Neuroendocrine & autonomic nervous system	19,542,000	20,356,000	+814,000
Learning, language and behavior	7,218,000	7,519,000	+301,000
Nervous system function	58,427,000	60,861,000	+2,434,000
Metabolism and nutrition	2,823,000	2,941,000	+118,000
Neurosensory disorders	14,169,000	15,601,000	+1,432,000
Multicategorical research	4,904,000	5,108,000	+204,000
Total	261,614,000	273,354,000	+11,740,000

National Institute of Neurological Disorders and Stroke

Clinical Research

Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$143,208,000	$148,330,000	+$5,122,000

Purpose and Method of Operation

Clinical research uses the fundamental knowledge developed by basic research to clarify pathological conditions and to identify and pursue methods for amelioration, therapeutic intervention, and prevention of these conditions. Studies involve not only clinical investigations in humans, but also preclinical research aimed at development of disease models as well as development of a variety of diagnostic tests and prosthetic devices. The purpose of this research is to identify means for eliminating the causes of disorders or to provide more definitive treatment of these disorders. This program activity is supported through research grants, research centers, research and development contracts, Research Career Program awards, and National Research Service Awards.

The Institute provides clinical research training through individual National Research Service Awards (postdoctoral fellowships) and institutional National Research Service Awards (training grants). These programs train personnel for academic careers in research aimed at developing improved diagnosis, treatment and, where possible, prevention of human nervous system disorders.

The Research Career Program, through Clinical Investigator Development Awards (CIDA), promotes and supports the development of research skills among physician scientists. This program seeks to recruit and prepare future physician investigators for academic research careers in the neurological sciences. This award provides candidates with the opportunity for 3-to-5 years of special study and supervised experience tailored to individual capabilities and research interests. These awards bridge the gap between the early postdoctoral period and academic appointment.

Rationale for the Budget Request

The 1991 request is $148,330,000, an increase of $5,122,000 over the 1990 appropriation. The following are the program plans for 1991:

Extramural Research

Diabetics who have undergone pancreatic transplantation are being followed to determine the effect of this procedure on the development of diabetic neuropathy. It is hypothesized that pancreatic transplantation will not only normalize blood sugar levels but also delay the development of the neuropathic symptoms commonly seen in diabetes.

A comprehensive epidemiological study of diabetic patients is examining the frequency, severity, and characteristics of neuropathic symptoms. Risk factors for the development of neuropathy, including the kind and duration of diabetes, type and control of therapy, hypertension, and kidney failure are being determined in a defined population.

The possible relationship between dietary deficiencies and neural tube defects--such as spina bifida-- is of longstanding interest. In the last few years, several studies have offered conflicting evidence on the protective effect of dietary or supplemental folate in reducing the risk of neural tube defects. Very recently, a new study involving over 20,000 pregnant women indicated that the prevalence of neural tube defects among women who used folic acid-containing multivitamins during the first six weeks of pregnancy was substantially lower than that among those who did not consume supplements. These studies are stimulating questions about the mechanistic role of folate and other nutrients in neural tube formation, and genetic and metabolic differences in the utilization of nutrients among pregnant women and their offspring. They also are pointing to the need for more refined studies examining possible relationships between specific types of neural tube defects and various environmental exposures, including nutrient intakes.

A human gene for torsion dystonia--a neurological movement disorder characterized by sustained muscle contractions, frequently causing twisted and repetitive movements, or abnormal postures--has been located on chromosome 9q32-q34. As many as 70,000-100,000 North Americans are affected with dystonia, and about half of these cases are believed to be hereditary. Understanding the molecular basis of hereditary dystonia has been difficult because only a limited number of neurochemical and neuropathological studies have been performed, and these have involved mixed patient populations expressing both hereditary and non-hereditary forms of the disease. Delineation of the genomic region containing the dystonia gene could lead to the discovery of the gene itself and its protein product, and also provide additional insights into the number of other genes possibly involved with hereditary dystonia.

Status epilepticus is a medical emergency in which a patient experiences continuous or repetitive seizures without full recovery of consciousness. Brain damage or death may occur if therapy is not prompt and effective. A new project has identified approximately 65 patients who have been prospectively enrolled in a study that will develop a mortality/risk scale. This work will permit the first epidemiological study on status epilepticus in a university and community setting with a validated data base to identify risk factors and to evaluate the efficacy of various treatments.

The pathophysiology of the epileptic focus in man remains unclear. The EEG, which measures voltage changes, continues to be the principal means of studying epileptic brain activity and visual inspection and qualitative description have been the chief means of EEG data analysis and presentation. However, a new technique called magnetoencephalography (MEG) which measures the changes in magnetic fields produced by brain neurons has been developed. Investigators are now correlating these techniques to provide better localization of deeply located epileptic foci within the brain.

Early and accurate diagnosis is important in the study of AD. Patients with this disease have greater difficulty recalling objects than in remembering locations. This finding and others will be used to develop a complete behavioral profile that may aid in the early diagnosis of AD.

The cause of motor neuron diseases (MND) such as amyotrophic lateral sclerosis (ALS) is unknown. Autoimmune, viral, toxic, metabolic, and traumatic etiologies have been suggested. Recently, elevated levels of antibodies were found that reacted with molecules called gangliosides that are present on the surface of nerves. Many people without disease have low levels of anti-ganglioside antibody. These antibodies were twice as common in patients with MND than in control subjects. The possible relationship between some motor neuron diseases and nerve specific antibodies is a stimulus for ongoing studies regarding a possible immune basis for these diseases.

The dramatic results obtained in the large multi-center clinical trial of deprenyl in Parkinson disease patients have encouraged continuation of the trial to determine the effect of long term deprenyl treatment in association with L-DOPA therapy, and the possible additional benefit of the anti-oxidant, Vitamin E.

There is controversy regarding the efficacy of reduced dietary protein intake to improved response to levodopa in Parkinson Disease patients. Further work will be done better to establish the nature of the relationship of dietary protein to levodopa treatment.

Preliminary trials with beta-interferon have suggested that this agent may be effective in decreasing the numbers of relapses in patients with multiple sclerosis (MS). A four year multicenter, randomized, double-blind, placebo-controlled clinical trial of recombinant beta-interferon will be undertaken in patients with relapsing MS.

In the study of Huntington's disease (HD), correlations between the age of onset, rate of progression, and neurogeneration of the brain will be explored. Behavioral manifestations of the disease such as anger, depression, manic symptoms, and suicidal thoughts will be examined and compared in men and women. Drugs that attenuate neurotoxic effects will be tested to assess their ability to retard neural degeneration and clinical decline. Studies to determine and lessen the negative psychological impact of presymptomatic testing of HD patients have been promising and will be expanded.

The search for additional markers for the HD gene will continue, aimed at eventual localization and cloning of the causative gene. Ultimately, identification and cloning of the HD gene will lead to isolation of its products and an understanding of the pathogenesis of the disease.

Ataxias are a family of degenerative central nervous system disorders characterized by impairment of coordination. More than 60 types of hereditary ataxias have been identified and others occur sporadically. The search will continue for markers of this disease and for the responsible gene(s).

Friedreich's ataxia is an autosomal recessive disease with onset during adolescence. The underlying cause of the disorder is unknown. During an epidemiological study on Cyprus a large family afflicted with Friedreich's ataxia was identified. Evidence of a genetic defect on chromosome 9 was found. Molecular genetic analysis will be done to identify the responsible gene and its product.

A study to determine the utility of frequent imaging of the brain using magnetic resonance imaging (MRI) in MS patients is planned to start in FY 1990. Because of the great sensitivity of MRI to changes in the brain, many of which are without clinical expression, these observations may provide new insights into the pathological course of MS and the diagnostic value of this important imaging technology.

Indications are that stroke incidence appears to be increasing, despite the decrease in mortality reported, and, as the mean age of the population continues to increase, the population at risk for stroke is even greater. Data suggest that it is important to monitor patients for the presence of unrecognized and (or) mild elevations in blood glucose. Moreover, in patients who are not considered to be diabetic, subtle or unrecognized elevations in blood sugar may contribute to the establishment of recurrent stroke or TIA. Therefore, continued vigilance to identify risk factors through epidemiological studies is of utmost importance in preventing the incidence and disability from this major health problem.

A major gap in our knowledge concerns the differences in incidence and mortality in minority groups compared to non-minority populations. A new five-year study has begun on the recurrence of stroke in Black and Hispanic populations. Patients are now being enrolled and risk factors (including family history of stroke, diet, smoking, and blood glucose and cholesterol levels) will be evaluated in an effort to determine which factors are implicated in the occurrence of subsequent stroke. The results of this study could provide us with important information that can be used in the prevention of added stroke risk in these populations.

Heparinoid is a new drug derived from heparin. It can prevent the formation of blood clots within blood vessels, but has less risk of hemorrhage outside of blood vessels than the widely used heparin. In pilot studies completed recently, heparinoid was shown to be safe enough to give to stroke patients and there was some evidence that it might be an effective treatment for preventing the progression of brain injury after some strokes. A very large multi-center clinical trial has been organized to test whether heparinoid will significantly improve the outcome in patients after stroke. Neurological function and disability will be evaluated three months after stroke. Treated and untreated groups will be compared to see if there is any benefit. The entire study is planned to take five years with ongoing monitoring for safety and data accuracy.

Because of the apparent relative safety of tissue plasminogen activator (TPA) and the encouraging early improvement of some stroke patients in an NINDS pilot study, a clinical trial has been planned for a larger number of patients. Nine clinical centers will participate. Half of the patients must begin treatment within 90 minutes after stroke; the remainder within three hours. TPA is potentially one of the most useful agents for treatment of stroke; however, it must be shown that it can be given early enough and at high enough doses to dissolve blood clots, re-establish blood flow, and prevent permanent brain injury.

2. Research Training and Career Development

In the Research Career Program, the goals of the Clinical Investigator Development Award (CIDA) are relevant and important. Maintenance of a "critical mass" of clinical investigators needs continuing emphasis and funding by the NINDS. An earlier Teacher Investigator Development Award, the first such research award aimed principally at physicians, provided a productive mechanism for developing a much needed pool of capable investigators. Support will continue for the newer CIDA Program which offers the potential for increasing this cadre of investigators with the provision of more flexibility in fitting the award period to the needs of the individual.

National Institute of Neurological Disorders and Stroke

Clinical Research

	1990 Appropriation	1991 Estimate	Increase or Decrease
Impact Data			
Neurological disorders of early life	$14,055,000	$14,640,000	+$405,000
Neurological disorders of adult life	15,226,000	15,860,000	+634,000
Stroke	25,903,000	26,682,000	+759,000
Epilepsy	20,268,000	20,813,000	+545,000
Demyelinating disorders	13,319,000	13,874,000	+555,000
Neuromuscular disorders	9,580,000	9,979,000	+399,000
Infectious diseases of the central nervous system	3,272,000	3,381,000	+109,000
Trauma and injury	24,367,000	25,382,000	+1,015,000
Tumors	3,051,000	3,178,000	+127,000
Neuroendocrine & autonomic nervous system	1,079,000	1,124,000	+45,000
Learning, language and behavior	2,889,000	3,009,000	+120,000
Nervous system function	4,997,000	5,206,000	+209,000
Metabolism and nutrition	414,000	431,000	+17,000
Neurosensory disorders	2,793,000	2,893,000	+100,000
Multicategorical research	1,995,000	2,078,000	+83,000
Total	143,208,000	148,330,000	+5,122,000

National Institute of Neurological Disorders and Stroke

Intramural Research

Authorization: Indefinite

Budget Authority:

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
Total........	478	$64,439,000	481	$69,105,000	+3	+$4,666,000
HIV/AIDS.....	(40)	($4,742,000)	(40)	($5,012,000)	--	(+$270,000)

Purpose and Method of Operation

The mission of the NINDS Division of Intramural Research (DIR) is to conduct basic and clinical research on the structure, function and malfunction of the brain, spinal cord, ear, muscle and related body organs. These substantial efforts range from basic neurobiological research to clinical studies of newly developed medical and surgical therapies. The laboratories and research clinics are located mainly at NIH in Bethesda, Maryland.

The most extensively supported neurosciences disciplines are neurovirology, neuroimmunology, neurophysiology, neurochemistry, neuropharmacology, neurogenetics, neuropathology, neuro-otolaryngology, neuroepidemiology and biometry. Clinical investigation focuses on demyelinating, metabolic, degenerative, convulsive and neoplastic disorders of the nervous system. The program also contributes substantially to the future prevention of the neurological diseases through the research training given to young clinical and basic research scientists.

Rationale for the Budget Request

The 1991 budget request for intramural research is $69,105,000, an increase of $4,666,000 over the 1990 level.

The research planned for FY 1991 will continue to be based mainly on following leads and lines of research developed in earlier years and attempting to answer new questions raised by findings reported from our laboratories and related observations reported by investigators throughout the world.

The cloning and sequencing of genes which determine the structure of various peptide neurotransmitters and their precursors, receptors, enzymes, transport processes and structural proteins, as well as abnormal deposits (e.g. neurofibrillary tangles), will continue to be an active area of research. The regulation of the expression of these genes, the molecular structure of their products, and their relationship to growth, development, regeneration, and pathological processes will be explored. Reducing the molecular structure of enzymes, receptors, transport proteins, storage sites and antibodies allows a new approach to understanding how these complex structures interact and are affected by specific ligands, viruses and drugs. The targeting of specific sites resulting in diseases and dysfunction as well as physiological regulation and rational therapeutic intervention will be better understood.

Large scale DNA sequencing has been developed to the point where it is feasible for the first time to sequence large chromosome regions.

As part of the plans to utilize newly developed, rapid sequencing of nucleotice bases, two collaborative efforts on neurological disease genes are being pursued. The first involves a collaboration with the Huntington's disease consortum to sequence the chromosome region associated with this disease. The sequence and our clones are being made available to the Huntington's group to be used as new probes in mapping the disease locus. The second collaborative effort is to sequence the chromosome region associated with von Recklinghausen's neurofibromatosis (NF1).

Direct enzyme replacement therapy for Gaucher's disease requires large amounts of expensive enzyme. Attempts will be made to determine the minimal required doses, to find a means of prolonging and potentiating the actions of the enzyme, and to develop other approaches to enzyme replacement such as use of retroviral vectors that carry a functional gene for glucocerebrosidase to transfer the gene to bone marrow stem cells which can be implanted in the patients.

Transgenic mice which mimic human metabolic storage disorders, such as Gaucher's disease, will continue to be used to examine new potential therapies.

Studies on Type C Niemann-Pick disease will continue to explore how the molecular defect causes the abnormal intracellular processing of cholesterol in patients. Measures will be developed to reduce the amount of cholesterol available to cells as a treatment for patients with this disorder.

Enzyme replacement in animal model of human generalized gangliosidosis will continue to be explored following temporary opening of the blood-brain barrier in these animals. These studies will determine the feasibility of enzyme replacement in humans with metabolic storage disorders involving central and peripheral nervous systems.

Mechanisms of regulation of formation of amyloid precursor and means of early detection of patients with Alzheimer's disease will continue. The search for growth factors and other biochemical determinants of growth, development and regeneration of axons should provide new potential approaches to therapy of degenerative diseases; studies of myelin components may unravel the processes by which mylenation occurs during development, demylination is induced in viral and immunological disorders, and remyelination may be induced.

The new methods (e.g. PCR, in situ hydridization) which are available for detection of viral protein will be applied to further understand the mechanism of viral entry, targeting of specific cells, regeneration and indication of pathological changes.

Further development of toxic destruction of specific neurons (with aluminum or other metals, diphtheria toxin, etc.) may provide useful animal models of human degenerative neurological diseases to test new therapies. Potential of placental tissue for implants to stimulate growth of dopaminergic neurons will be further explored in the MPTP model of Parkinsons disease. Investigators will continue the efforts to identify and characterize growth factors which may enhance sprouting of new nerve axonal processes into areas of damage or may regulate development of the nervous system.

Methods for examining brain plasticity after stroke or trauma will be further refined and if quantification proves reliable, therapeutic efforts will be directed towards promoting recovery.

Distinctions among patients with autoimmune neuropathy will be explored for clues to new approaches for better management of patients with these disorders.

Clinical studies of new agents for management of epilepsy and treatment of patients with metastatic invasion of the leptomeninges will be initiated. Several of the newer techniques for neuroimaging by PET (positron emission tomography) and MRI (Magnetic resonance imaging) will continue to be expanded to include new ligands and advanced detailed analysis to obtain information about transport, metabolic processes, neurotransmitters, receptors, blood brain barrier, etc., in health and disease. These techniques find wide application because they provide directly information about physiological processes in the brain of living humans. Such information was previously unavailable or available only after death.

National Institute of Neurological Disorders and Stroke

Research Management and Support

Authorization: Indefinite

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
187	$20,079,000	187	$21,423,000	--	+$1,344,000

Purpose and Method of Operation

This activity includes the extramural program directors and their staffs who are responsible for the scientific planning, direction, administration, and review and approval functions of their program's research grant, research contract, and research training programs. The Division of Extramural Activities staff are responsible for the Institute's overall grants and contracts administration including processing, award and management activities. This activity also supports the immediate Office of the Director, and the staff which assists the Director in management and direction of the Institute's programs. These units include the administration and financial management activities of the Institute as well as program analysis functions and scientific and health reporting.

Rationale for the Budget Request

The 1991 budget request for research management and support is $21,423,000, an increase of $1,344,000 over the 1990 comparable level.

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Detail of Permanent Positions

	1989 Actual	1990 Appropriation	1991 Estimate
ES-5	1	1	1
ES-4	13	13	13
ES-3	1	2	2
Subtotal	15	16	16
GS/GM-15	24	24	24
GS/GM-14	38	38	38
GS/GM-13	38	39	39
GS-12	30	32	32
GS-11	55	55	55
GS-10	2	2	2
GS-9	55	57	57
GS-8	12	12	12
GS-7	56	58	58
GS-6	37	37	37
GS-5	31	33	33
GS-4	9	10	10
GS-3	5	5	5
GS-2	1	1	1
Subtotal	393	403	403
Grades established by Act of July 1, 1944 (42 U.S.C. 207)			
Assistant Surgeon General	1	1	1
Director Grade	19	20	20
Senior Grade	6	8	8
Full Grade	2	3	3
Senior Assistant Grade	--	1	1
Subtotal	28	33	33
Ungraded	9	9	9
Total permanent positions	445	461	461

NATIONAL INSTITUTES OF HEALTH

National Institute of Neurological Disorders and Stroke

Advisory and Assistance Services

For FY 1991, the NINDS Advisory and Assistance Services budget will be $14[illegible],000, an increase of $20,000 over 1990. These funds will support a variety of services that will include the following activities:

Personnel appointments represent salaries paid to members of the Institute's National Advisory Council (NANDS) and to the members of the Board of Scientific Counselors in the Division of Intramural Research.

Individual experts and consultants attend meetings of the clinical and data safety monitoring committees of the extramural divisions, meetings of ad hoc program advisory committees, and meetings to conduct technical merit review of contract proposals.

The major portion of the consultant services funds are used for the peer review of our grants and contracts. The NIH Peer Review System is based on statutory authority; therefore, participation by outside consultants is mandatory. Other experts and consultants are employed to share technical knowledge and expertise of a scientific nature with Institute scientists on the latest developments in critical areas of NINDS research. These scientific symposiums provide NINDS scientists with additional clues to assist them in finding the key to prevention and treatment of the many baffling neurological disorders.

The yearly increases are due to an ever increasing load in the number of grant applications and contract proposals. If we are to maintain our high quality of grant and contract review and administration, such increases are essential.

Consultant services contracts under $3,000 requested by Institute staff must be approved by the Principal Administrative Officers; those over that amount are subject to NIH approval. Principal Administrative Officers must complete training to receive their approval authority and all approved orders are subject to audit by Institute management.

WEDNESDAY, MARCH 14, 1990.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

WITNESSES

DR. ANTHONY S. FAUCI, DIRECTOR

DR. WILLIAM F. RAUB, ACTING DIRECTOR, NIH

DR. JOHN W. DIGGS, DIRECTOR, DIVISION OF EXTRAMURAL ACTIVITIES, NIAID

MICHAEL I. GOLDRICH, EXECUTIVE OFFICER, NIAID

STEVEN J. BERKOWITZ, FINANCIAL MANAGEMENT OFFICER, NIAID

DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. NATCHER. At this time, we take up the budget request for the National Institute of Allergy and Infectious Diseases, and we have before the committee Dr. Fauci.

Dr. Fauci, you have appeared before our subcommittee on a number of occasions; it is a pleasure to have you back again today, and before you give us your statement, tell us who you have with you at the table, please.

Mr. CONTE. Mr. Chairman, before he does that, Doctor, I have an appointment with Chairman Whitten, it is a supplemental, and I have to go over there.

I just want you to know why I am leaving, otherwise I would stay right here.

Mr. NATCHER. Okay. Go right ahead, Doctor.

Dr. FAUCI. Thank you very much, Mr. Chairman.

It is a pleasure to be here. I have with me Dr. John Diggs, Director of our Division of Extramural Activities; Mr. Michael Goldrich, Executive Officer of the Institute; and on my right, Mr. Steven Berkowitz, who is the Chief of the Financial Management and Information Systems Branch of the Institute; and you know Dr. Raub and Mr. Williams.

Mr. NATCHER. We are delighted to have all of you before the committee, and Doctor, we will be pleased to hear from you at this time.

Dr. FAUCI. Mr. Chairman, I have submitted my written statement for the record.

I would like to spend just a few minutes using my illustrations to highlight some of the points which I have made in that written statement.

Mr. NATCHER. Go right ahead, Doctor.

OPENING STATEMENT

Dr. FAUCI. On past occasions, I have come before this committee and emphasized the Institute's commitment to basic research on immunology and microbiology as what we have called an investment in the future.

Looking in terms of decades, the investments that we made in the seventies have yielded results, and important discoveries in the eighties, and we hope that what we have done in basic research in the eighties will yield important fruits in the 1990s.

Using this cartoon illustration, we show how basic research can yield things like diagnostics, vaccines, new treatments and organ transplantation; in essence, we are putting money in the bank for the future as shown in illustration 1.

[Chart follows:]

Basic Research in Immunology and Microbiology as an Investment in the Future

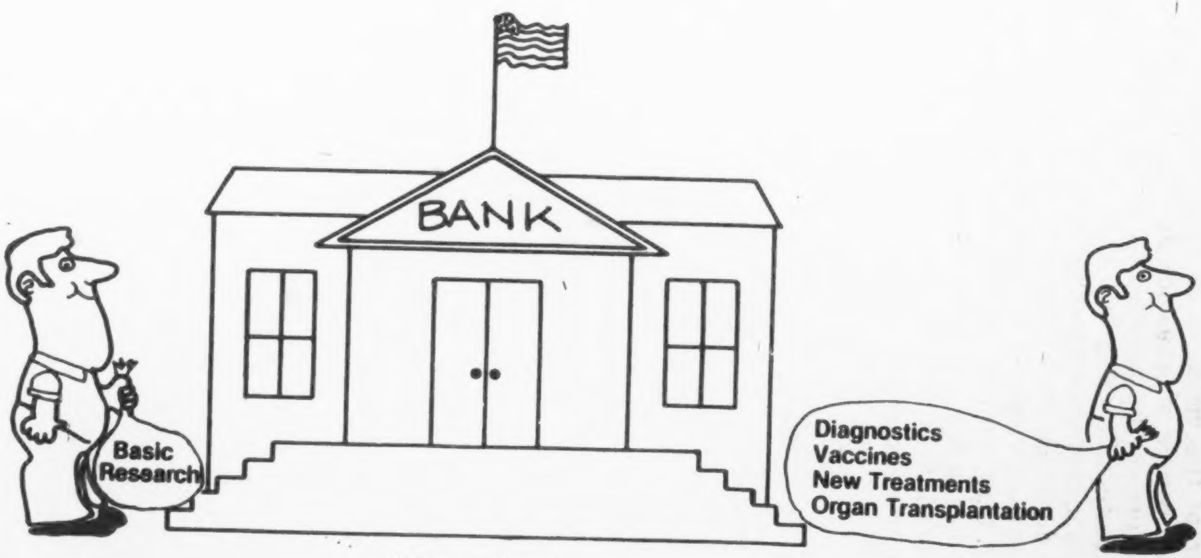

BANK
Basic Research
Diagnostics
Vaccines
New Treatments
Organ Transplantation

Illustration 1.

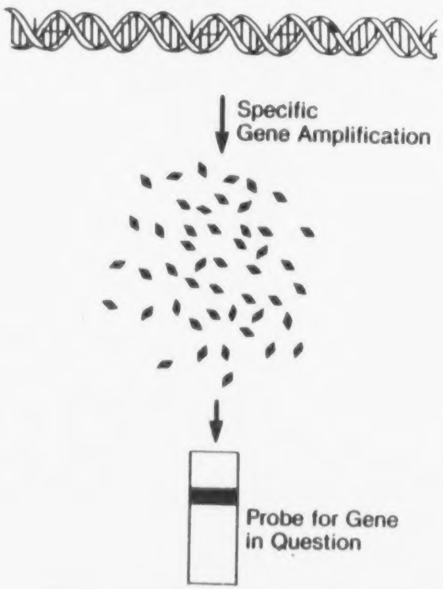
One of the yields of basic biomedical research has been alluded to on a couple of occasions during these hearings thus far, and that is the use of the polymerase chain reaction or the gene amplification technique to detect very small amounts of genetic material that is mixed up with other large amounts.

As demonstrated here in illustration 2. For example, if a gene of interest is contained in a genome in a cell, you would not be able to detect that, unless you very specifically amplified that one particular gene, making it in sufficient quantities that you can use genetic probes to identify it.

[Chart follows:]

Polymerase Chain Reaction (PCR) — Gene Amplification

Technique


Specific
Gene Amplification
Probe for Gene
in Question

PCR Applications

Infectious Diseases—Diagnosis
- AIDS
- Lyme disease
- Chlamydial infections

Transplantation
- Donor/recipient matching

Basic Research
- Gene sequencing
- Molecular genetics

Forensic Medicine

Illustration 2.

Last year, before this committee, I mentioned to the group how we have been using this to diagnose AIDS in patients who have very little virus in their cells. You have probably read most recently in the newspapers that now we are using the technique to diagnose Lyme disease in individuals in whom the diagnosis has been elusive because of the insensitivity of the diagnostic tests.

We don't have time to go over many of the other uses for it, but let me tell you why this is so important with Lyme disease. Lyme disease, as you know, has become a very important disease in the United States, with the number of cases increasing at an alarming rate as reflected here in illustration 3.

[Chart follows:]

Reported Cases of Lyme Disease, by Year - United States, 1982-1988

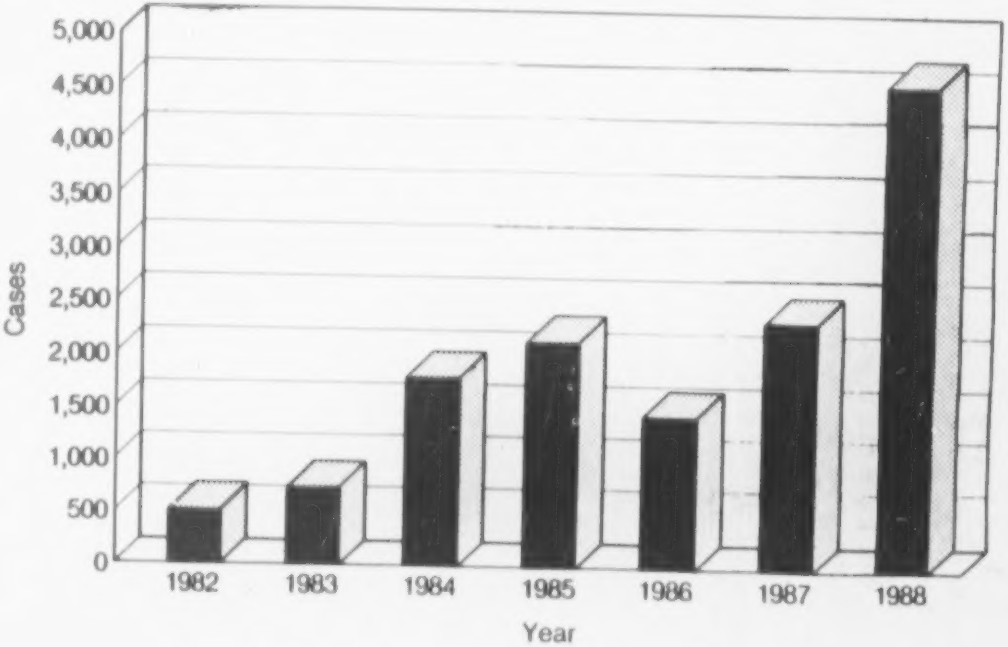


Illustration 3.

Officially, there have been approximately 5,000 cases in 1988, but most experts agree that, in fact, the number is probably several-fold. The reason is that there are many individuals with chronic disease very likely caused by the Lyme disease agent *Borrcelia burgdorferi*, but have not been diagnosed.

Using the polymerase chain reaction technique, we have now been able to identify the genetic material from in the microorganism in individuals who have suffered for years from what had been considered up to that point chronic disease. I think this is going to be an important breakthrough that will bring further development in the nineties.

Another very important area is the elusive non-A, non-B hepatitis virus, which we now call hepatitis C shown here in illustration 4.

[Chart follows:]

The Elusive Non-A, Non-B Hepatitis Virus: Hepatitis C

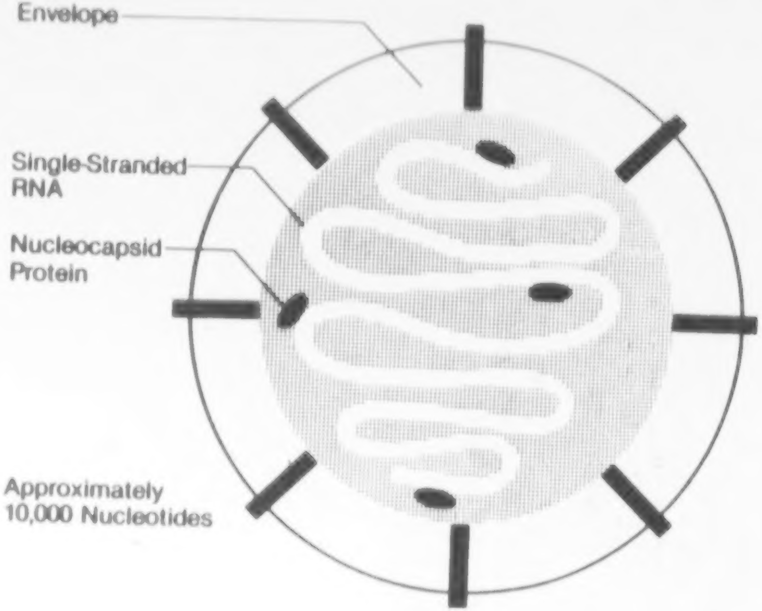

Envelope
Single-Stranded RNA
Nucleocapsid Protein
Approximately 10,000 Nucleotides

Illustration 4.

This virus is currently the major cause of transfusion-related hepatitis in the United States, anywhere from 200,000 to 300,000 cases per year, approximately 50 percent of which progress to chronic liver disease.

Using a genetic engineering approach, and the ability to identify specific antigens on the surface of this microorganism, scientists have been able to devise a diagnostic test that hopefully, in the nineties, will be routinely implemented.

This is very exciting, because now we will be able to screen blood for hepatitis C. We have been able to eliminate hepatitis B from the blood transfusion pool. Hopefully we will do the same with hepatitis C.

I would like to describe here in illustration 5 some very interesting advances that have been made in AIDS since I last appeared before this committee.

[Chart follows:]

Therapeutic Advances in AIDS

- Early intervention
- Lower dose of AZT
- Aerosolized pentamidine approved for prophylaxis of pneumocystis pneumonia
- Ganciclovir approved for CMV retinitis
- Erythropoietin approved for anemia in AIDS patients
- 35-40 drugs in clinical trials

Illustration 5.

You have probably read in the press the concept of early intervention using a lower dose of AZT. We now know, because of studies that were conducted at NIAID's clinical trials group, that one can use half the dose of AZT, and if you use it early in individuals who have absolutely no indication at all of being ill, but who are infected with HIV, you can delay the onset and the progression of symptoms.

We now have prophylaxis against some of the important complications of AIDS: aerosolized pentamidine for pneumocystic pneumonia; gancyclovir for the eye disease retinitis, which is such a terrible complication of HIV infection; and erythropoietin, which is used for anemia.

Of particular importance, approximately 35 to 40 drugs are being tested alone or in combination, in clinical trials in our AIDS clinical trials group. In the past year, we have established our community programs for clinical research on AIDS. Eighteen community programs are located throughout the country with the specific objective of bringing clinical trials to the grass-roots community level. This is going to have an important impact on making clinical trials accessible to traditionally underserved populations: women, minorities, and children. Individuals who are under-represented in our secondary and tertiary clinical trial settings.

As you can see in illustration 6, it has been a very good year with regard to HIV vaccine development.

[Chart follows:]

HIV Vaccine Development

- Immune response to HIV
- Phase I trials in humans
- Successful protection of monkeys in SIV vaccine studies

Illustration 6.

The immune response to the virus been delineated, and we have continued our phase one trials. Most importantly over the past summer and fall, three separate studies have indicated successful protection of monkeys from a simian immunodeficiency virus, which is analogous to human immunodeficiency virus.

These establish for the first time the feasibility of being able to develop an AIDS vaccine for humans. You might remember last year before the committee, I mentioned that I wasn't even sure if we ever would have a vaccine.

Basic science has told us the good news is that a vaccine is possible and I hope that sometime in the decade of the nineties, I will be able to report its development to this committee.

With regard to vaccines, they have eliminated or dramatically reduced a number of diseases in the United States and the world, diseases that you are very familiar with, like measles, smallpox, and polio. Yet, a number of other diseases remain as reflected here in illustration 7, such as hemophilus influenzae B, which causes bacterial meningitis in young children, and group B strep, which causes permanent disability in half of the infants who get infected.

[Chart follows:]

Childhood Diseases Preventable by Vaccines in the 1990s

- *Hemophilus influenzae* B
  - — Most common cause of bacterial meningitis in young children
- Group B streptococcus
  - — Causes death or permanent disability in half the affected babies
- Rotavirus
  - — Worldwide, leading cause of diarrheal deaths in infants
- Respiratory syncytial virus
  - — The major cause of croup & pneumonia in infants
- Parainfluenza viruses
  - — A major cause of croup in children; important cause of pneumonia in young infants

Illustration 7.

We do not yet have vaccines widely available for these diseases, and again, hopefully I will be able to come back to you in the nineties and tell you that we can prevent and perhaps eliminate one or more of these diseases.

And finally, let me just close on a note that was introduced at this committee over a decade ago. Many of you remember my predecessor, Dr. Richard M. Krause, the former Director of NIAID, who wrote a book called, "The Restless Tide: The Persistant Challenge of the Microbial World." We used that analogy to indicate that here in our lives, we are constantly bombarded by waxing and waning tides of microorganisms demonstrated here in illustration 8.

[Chart follows:]

Restless Tide of Diseases

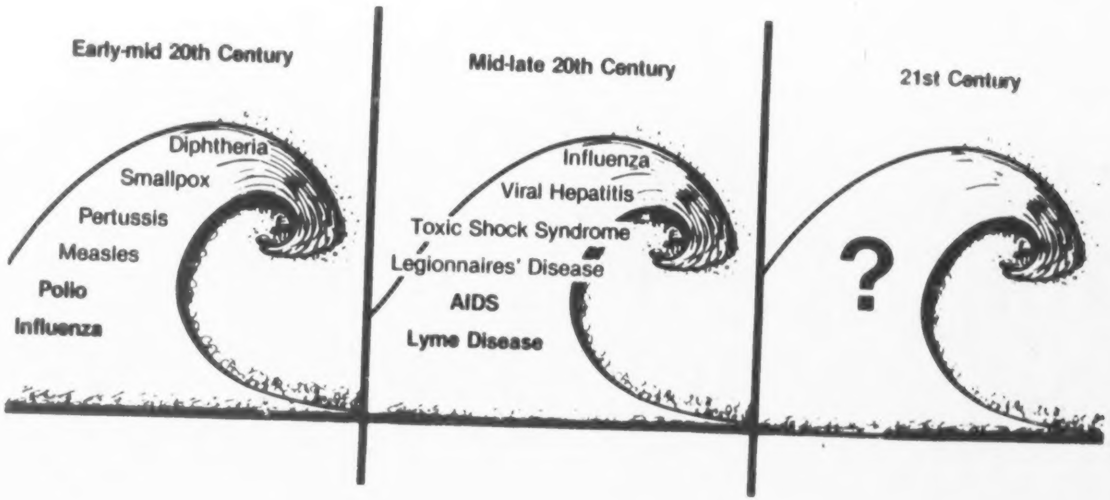

Early-mid 20th Century
Diphtheria
Smallpox
Pertussis
Measles
Polio
Influenza
Mid-late 20th Century
Influenza
Viral Hepatitis
Toxic Shock Syndrome
Legionnaires' Disease
AIDS
Lyme Disease
21st Century
?

Illustration 8.

If one looks back historically over the years, to the early and mid-20th century, several diseases that plagued mankind: there was polio; the terrible influenza epidemic of 1918; and other diseases like pertussis and measles.

As those diseases were brought under control in the middle and late 20th century, new diseases emerged that we had never heard of before: Legionnaire's disease, toxic shock syndrome, Lyme disease and, of course, AIDS, which has become such a terrible scourge.

Certainly in the 21st century, this restless tide and its cauldron of microorganisms will continue to challenge us.

I can't tell you now in 1990 the nature of these organisms, that are going to be in this restless tide of the 21st century, but almost certainly they will occur. It is our commitment to basic biomedical research that has allowed us to overcome these organisms in the past. Hopefully, with the commitment that we have to basic biomedical research, immunology and infectious diseases, we will be able to stem this inevitable tide.

Thank you, Mr. Chairman. I would be happy to answer any questions.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute of Allergy and Infectious Diseases

We live in an era of great scientific accomplishments, but it is also an era of unprecedented emerging research opportunities. These opportunities have been made possible in large part by advances in biotechnology and molecular biology, many of which are the fruits of NIAID-supported basic research. Without question, we are now reaping the benefits of our investment in basic research of past decades. Likewise, the basic research of today is a vital investment in the accomplishments of tomorrow.

In particular, during the decade of the 1980s, the rapidly evolving fields of immunology and microbiology have provided new opportunities for creative and high-yielding research. For example, last year I mentioned a new research technique called the polymerase chain reaction, or PCR, that uses the polymerase enzyme from a microorganism living in the warm waters of geysers and hot springs. I explained how PCR can multiply minute quantities of genetic material in a tissue sample, making it possible to detect disease-causing microorganisms that otherwise are hidden in the human body. Researchers who were working on the microbiology and molecular biology of that unusual bacteria called Thermus aquaticus had no idea of the ultimate implications of their research.

Over the past year, AIDS research has brought PCR to the forefront where it has been used to detect very early HIV infection. In fact, its value is much broader than AIDS diagnosis, and NIAID intramural scientists have been among the first to explore its possibilities. They have adapted PCR to a diagnostic test for the elusive agent of Lyme disease. Carried by ticks and recognized only 15 years ago, Lyme disease is now the most commonly reported arthropod-borne disease in the United States. If not treated, it can cause great pain and disability from chronic arthritic, neurologic, or cardiac symptoms. A major roadblock to effective treatment has been the lack of reliable tests to diagnose the disease during early infection. Development of a sensitive new test using PCR should greatly facilitate accurate diagnosis.

Another important accomplishment of the 1980s was built on basic research by NIAID intramural scientists. In the 1970s, they identified an agent that they called non-A non-B hepatitis virus and determined that it was the principal cause of transfusion-associated hepatitis. They characterized the agent by extensive basic research studies using chimpanzees, the only animal host other than man susceptible to the agent. Using this information, other scientists in 1989 succeeded in developing a test that, for the first time, detects individuals who are infected with the agent, now called hepatitis C virus. The test will make it possible to screen blood donors and prevent transmission of hepatitis C, which often leads to chronic hepatitis and, in some cases, to cirrhosis and liver failure.

Particularly noteworthy in its ability to create and capitalize on research opportunities that impact on many scientific disciplines, the NIH intramural research program allows established investigators to work in an undistracted environment that allows for intellectual risk-taking. Basic and clinical research are linked in a manner that makes possible a rapid response to emerging problems. In addition, it has provided training for many, if not most, of the outstanding biomedical research scientists in the United States. In fact, two winners of the 1989 Nobel Prize in Physiology and Medicine were trained at the NIH, one in the NIAID intramural program. This investment has enabled the United States to take the leadership role in biomedical research, particularly in immunology, microbiology, and AIDS research.

One exciting example of the dividends of basic research in immunology is the emergence of new insights into the immune mechanisms and cell types involved in the rejection of organ transplants. Scientists now have a sound basis for developing immunosuppressive agents that are more effective and less toxic than those presently in use. Recently, NIAID grantees produced a hybrid molecule linking diphtheria toxin to interleukin 2, one of several powerful chemical substances known as cytokines that are produced by the immune system. This molecule carrying its toxic ammunition acts as a "magic bullet," specifically binding to and eliminating the cells responsible for transplant rejection. This is only one of several new immunosuppressive measures being developed to improve the success rate for organ transplantation.

Other cytokines also hold promise as therapeutic agents. We reported last year that NIAID investigators showed that interleukin 4 was a potent inducer of the IgE molecule, which triggers allergic and hypersensitivity reactions. These scientists have now prevented the elevation of IgE levels in animals by administering a monoclonal antibody that binds to interleukin 4 and thus blocks its ability to stimulate IgE production.

Monoclonal antibodies, developed in the 1970s, provide another example of how the investment in basic research is paying off today. In the 1980s, monoclonal antibodies opened the door to remarkable new approaches to preventing, diagnosing and treating disease, and the benefits will continue to multiply in the 1990s and well into the next century.

Nowhere do we have better examples of the payoffs from basic research investments than in AIDS research. The advances in understanding AIDS have been extraordinary, and 1989 alone has produced results from several important studies that may mean longer and healthier lives for those infected with the AIDS virus and bring us closer to development of an effective vaccine.

Two NIAID studies have shown the value of early intervention in treating persons infected with the human immunodeficiency virus

(HIV). These studies showed that AZT, the antiviral drug approved in 1987 for treatment of persons with AIDS, significantly slows progression of disease in people who are infected with the virus and whose levels of T4 cells have declined modestly, but who have no symptoms or have the earliest symptoms of HIV infection.

These results strengthen the argument that early recognition of infection can be extremely beneficial since a doctor can closely monitor the immune system of the infected person and advise early treatment with AZT, other antiviral drugs, or drugs to prevent opportunistic infections.

A third NIAID study revealed that AZT was as effective and less toxic at half the dose originally recommended. As a result, the FDA in January 1990 approved changing the labeling for the drug. By using a lower dose, fewer patients may have to discontinue AZT therapy because of serious side effects.

In the meantime, the number of drugs being studied in AIDS clinical trials continues to climb--approximately 35 drugs or combinations of drugs are presently being tested by NIAID-supported investigators in more than 100 studies being done in 47 AIDS Clinical Trials Units throughout the United States. Fifteen of these Units conduct clinical trials exclusively in children, and seven of the adult Units also do pediatric studies.

The results reported last year show the importance of carefully controlled clinical trials. To HIV-infected persons, trials also mean earlier access to promising drugs. To expand that opportunity to those under- represented in trials in the past, NIAID has funded 18 Community Programs for Clinical Research on AIDS. These programs, conducted at the grass roots level, complement the AIDS Clinical Trials Units at large academic medical centers. They reach out to HIV-infected blacks, Hispanics, i.v. drug users, and women in 14 American cities where the impact of AIDS is severe.

Patients seeking access to clinical trials usually ask--Where can I go to enter a trial? What drugs are being tested for someone with my symptoms and stage of disease? In order to provide that information quickly and easily to any interested person, NIAID cooperated with other Public Health Service agencies to establish the AIDS Clinical Trials Information Service in May 1989. By dialing 1-800-TRIALS-A, the caller reaches a trained specialist who gives information about NIH-sponsored as well as other trials.

AIDS vaccine research took a significant step forward this year. Findings from several animal studies have dispelled early doubts about the scientific feasibility of an AIDS vaccine. In these studies, a prototype AIDS vaccine made from a virus that infects rhesus monkeys has protected the animals from getting AIDS. Also, the monkeys protected by the vaccine give researchers a long-awaited opportunity to study an AIDS-resistant immune system in order to characterize the biological features responsible for warding off the infection.

As you can see, we are beginning to reap dividends from the intensive investment in AIDS research, an investment that will have a positive impact not only in AIDS, but also in other areas of research. For example, research on antivirals and other antimicrobial agents, given great impetus by the AIDS epidemic, will in the 1990s lead to treatments for other sexually transmitted viral diseases and for the opportunistic infections that take the lives of so many immunosuppressed cancer patients and organ transplant recipients.

In the last few years, basic research has provided us with an increasingly sophisticated understanding of infectious agents, of the immune system's remarkable capacity to produce powerful, appropriate and self-limiting responses to infection, and of the diseases that can affect the immune system itself. This understanding has been responsible for the remarkable progress in AIDS research. It has also presented biomedical science with an extraordinary array of emerging opportunities. As a scientist and administrator, I must constantly set priorities after carefully considering the opportunities for progress and the urgency of the problem.

One urgent problem we face in this country is the disproportionate number of primarily black and Hispanic children in the inner cities who are suffering and dying from asthma. There is mounting evidence that asthma mortality and morbidity rates are increasing in the United States, despite advances in therapeutics and development of patient-education strategies. These rates are particularly high in the inner cities. NIAID will fund a network of centers as part of a national cooperative inner-city asthma study. These centers will determine the most effective ways to reduce asthma morbidity in these children.

Another urgent problem that I have discussed in past years is the terrible toll taken by sexually transmitted diseases particularly on young women, in whom we are seeing increases in infertility, and on babies, who are often left mentally retarded or otherwise impaired by infection before and during birth. Today, achievements in basic research provide emerging opportunities to develop vaccines and improve diagnostic tests and treatments for many of these diseases. To take advantage of this, NIAID will fund STD Cooperative Research Centers.

NIAID is in a unique position among NIH Institutes to use the emerging opportunities in biomedical research to provide the means to prevent and even to completely eliminate certain diseases from the United States and the world. Availability and strategic use of a vaccine eliminated one of the most severe infectious diseases, smallpox, from the entire world. The combined use of vaccines and antibiotics has dramatically reduced the impact of other infectious diseases, such as polio, diphtheria, pertussis, and rubella. In addition, we are now able to predict with some certainty the year-to-year changes in the influenza virus and design a protective flu vaccine.

However, worldwide, the toll of human life and suffering brought by other infectious diseases, such as malaria, filariasis, schistosomiasis, and hepatitis, remains staggering. In the United States, influenza and pneumonia continue to affect millions of people and are still the sixth leading cause of death; measles and tuberculosis are re-emerging; and Hemophilus influenza B and Group B streptococcus cause permanent disability in thousands of young children each year. In addition, newly recognized diseases are sweeping in to challenge us--Lyme disease, Legionnaire's disease, and--most recently and most devastating--the AIDS pandemic.

We at NIAID look to the decade of the 1990s with enthusiasm, energy, and resolve. I am confident that we can meet the challenges of the 1990s through the knowledge that we have gained and will continue to gain through investments in basic and clinical research. Such is the nature of biomedical research. Its dividends may be unpredictable, but they are inevitable.

Mr. Chairman, the FY 1991 budget request for this Institute is $886,875,000. I will be pleased to answer any questions you may have.

FAUCI, DR. ANTHONY S.
Director, National Institute of Allergy and Infectious Diseases

December 24, 1940. Brooklyn, New York

Education:

College of Holy Cross, 1962 - A.B.; Cornell University Medical College, 1966 - M.D.

Professional History:

1966-1967, Intern, Department of Medicine, New York Hospital-Cornell Medical Center. 1967-1968, Assistant Resident, Department of Medicine, The New York Hospital-Cornell Medical Center. 1968-1970, Clinical Associate, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, Maryland. 1970-1971, Senior Staff Fellow, Laboratory of Clinical Investigation, NIAID, NIH, Bethesda, Maryland. 1971-1972, Chief Resident, Department of Medicine, New York Hospital-Cornell Medical Center; Instructor in Medicine, Cornell Medical College. 1972-1974, Senior Investigator, Laboratory of Clinical Investigation, NIAID, NIH, Bethesda, Maryland. 1972-present, Consultant in Infectious Diseases, The National Naval Medical Center, Bethesda, Maryland. 1974-1980, Head, Clinical Physiology Section, Laboratory of Clinical Investigation, NIAID, NIH, Bethesda, Maryland. 1977-1984, Deputy Clinical Director, NIAID, NIH, Bethesda, Maryland. 1980-present, Chief, Laboratory of Immunoregulation, NIAID, NIH, Bethesda, Maryland. 1984-1988, Clinical Professor, Department of Medicine, Division of Rheumatology, Immunology, and Allergy, Georgetown University School of Medicine, Washington, D.C. 1985-1988, Clinical Professor, George Washington University School of Medicine and Health Sciences, Washington, D.C. 1984-present, Director, NIAID, NIH, Bethesda, Maryland. 1988-present, Director, Office of AIDS Research, NIH, and Associate Director of NIH for AIDS Research, Bethesda, Maryland.

Board Certification and Military Service:

American Board of Internal Medicine-June 21, 1972. American Board of Allergy and Immunology-March 1, 1974. American Board of Infectious Diseases-October 15, 1974. U.S. Public Health Service, July 1968-June 1970; July 1972-Present.

Professional Organizations:

American Federation for Clinical Research, American Association for the Advancement of Science, American Association of Immunologists, American Medical Association, Fellow of the American Academy of Allergy, Infectious Diseases Society of America, American Society for Clinical Investigation, Fellow of The American College of Physicians, Association of American Physicians, Collegium Internationale Allergologicum, Charter Member of the Clinical Immunology Society. The Institute of Medicine of the National Academy of Sciences (USA).

Offices Held:

Councillor, Eastern Section, American Federation for Clinical Research (AFCR), 1977. National Councillor, AFCR, 1978-1979. President, AFCR, 1980-1981. Recorder, Association of American Physicians, 1988-present.

Advisory Boards and Committees:

Chairman, Allergy and Immunology Committee, MKSAP V, American College of Physicians. Advisory Panel, The American Board of Medical Laboratory Immunology. Member, Committee on Clinical Immunology and Immunopathology, American Association of Immunologists, 1980-1985. Representative of American Association of Immunologists to the Examinations Committee of the American Board of Allergy and Immunology, 1981-present. Postgraduate Education Committee, American Academy of Allergy, 1979-1982. Member, NIAID Study Group on Immunology, 1980. Member, Section of Physiology in Clinical Science of the American Physiological Society, 1980-1984. Member, Subcommittee on the Classification of Vasculitis, American Rheumatism Association 1980-present. Ad Hoc Committee, The National Foundation for Infectious Diseases, 1980-present. Subcommittee on Clinical Sciences, Publications Committee, American Physiological Society, 1980-1984. American Association of Immunologists, 1982-1985. Member, NIAID Working Group for AIDS, 1982-present. Member, American Federation for Clinical Research President's Public Policy Advisory Committee, 1983-present. Board of Directors, American Board of Allergy and Immunology, 1984-1987. Participant in the USA - People's Republic of China Immunology Cooperative Agreement, August 10-22, 1983, Beijing and Shanghai, PRC. Member, Scientific Advisory Board, Medical Biology Institute, La Jolla, CA, 1983-1984. Participant in the USA-Japan Eye Immunology Advisory Conference, November 27 to December 1, 1983, Honolulu, HI. Member, External Advisory Committee, Multipurpose Arthritis Center, Duke University Medical Center, 1984-present. Member, Honorary Advisory Board, Italian-American Medical Association, 1984-present. Member, Peripatetic Club, 1984-present. Ex Officio Member, National Diabetes Advisory Board, 1984-present. Ex Officio Member, National Digestive Diseases Advisory Board, 1984-present. Chairman, Search Committee for Director, National Institute of Child Health and Human Development, 1985. Member, Department of Health and Human Services Task Force on Alzheimer's Diseases. The Albert Lasker Medical Research Award Jury, 1985-present. Deputy Ethics Counselor, Department of Health and Human Services, 1985-present. Member, Department of Health and Humans Services Committee to Coordinate Environmental and Related Programs, 1985-present. Member, Scientific Organizing Committee, Joint Meeting of the Italian Society of Immunology and Immunopathology-National Institutes of Health on "Human Lymphocyte Activation," Florence, Italy, September 5-7, 1985. Member, United States Delegation to the United States-Japan Cooperative Medical Science Committee, 1985-present. Member, U.S. Public Health Service AIDS Executive Task Force, 1985-present. Chairman, NIH AIDS Executive Task Force, 1985-present. Coordinator, NIH AIDS Research, 1985-present. Member, Scientific Seminar Subcommittee, National Institutes of Health Centennial Program, 1985-1987. Member, Advisory Board, Clinical Immunology Newsletter, 1986-1988. Member, Scientific Organizing Committee, International Conference on

Lymphocyte Activation and Immune Regulation, Newport Beach, CA, February 28-March 2, 1986. Member, Planning Committee, Clinical Immunology Society, 1986. Member, International Advisory Committee, International Conference on AIDS, Paris, France, June 23-25, 1986. Member, Advisory Group, Institut Scientifique Roussel-Uclaf, 1987-1989. Ex Officio Member, National Kidney and Urologic Diseases Advisory Board, 1987-present. Member, International Programme Committee, 8th International Congress of Immunology, Budapest, Hungary, 1987. Member, International Advisory Committee,IVth International Conference on AIDS, Stockholm, Sweden, June 12-16, 1988. Member, NIH Resource Allocation Group, 1987-1989. Member, Committee for the Coordination of Research Programs on the Acquired Immunodeficiency Syndrome of the Ministry of Health of Italy, 1988-present. Institute of Medicine Roundtable for the Development of Drugs and Vaccines Against AIDS, January 17, 1989, through December 31, 1991.

Editorial Boards:

Dr. Fauci has been or is on the Editorial Board of 27 scientific journals in the field of immunology, allergy and infectious diseases. These include: The Journal of Clinical Investigation, The Journal of Immunology, Journal of Infectious Diseases, Journal of Clinical Immunology. Dr. Fauci is also the Editor of one of the major textbooks of medicine in the world, "Harrison's Principles of Internal Medicine."

Awards and Honors:

Alpha Omega Alpha. Kileen Prize for Excellence in Chemistry (College of the Holy Cross). John Metcalfe Polk Prize for General Efficiency (Cornell University Medical College). Alfred Mortitz Michaelis Prize for Efficiency in General Medicine (Cornell University Medical College). U.S. Public Health Service Meritorious Service Award, 1979. Arthur S. Flemming Award, 1979 - Given to the 10 outstanding employees in the U.S. Federal Government. Squibb Award of the Infectious Diseases Society of America, 1983. U.S. Public Health Service Distinguished Service Medal, 1984. Food and Drug Administration Commissioner's Special Citation, 1984. 1985 Citation Classics (Current Contents) for article - A.S. Fauci, D.C. Dale, and J.E. Balow: Glucocorticosteroid therapy: mechanisms of action and clinical considerations. Ann. Intern. Med. 84: 304-315, 1976. Who's Who in America, 44th Edition. Who's Who in Science and Technology, 2nd Edition. 1985 Stanford University Center Survey of the American Rheumatism Association membership ranked the work of Dr. Anthony S. Fauci on the treatment of polyarteritis nodosa and Wegener's granulomatosis as one of the most important advances in patient management in rheumatology over the past 20 years. The Clemens von Pirquet Award of Georgetown University Medical Center, 1986. Doctor of Science, Honoris Causa, College of the Holy Cross, Worcester, MA May 29, 1987. The Kober Lecture Award of the Association of American Physicians, 1988. Public Health Leader of the Year Award of the Commissioned Officers Association of the U.S. Public Health Service, 1988. The National Institutes of Health Clinical Center Annual Distinguished Clinical Educator Award, 1988. 1988 Citation Classics (Current Contents) for article - A. S. Fauci, B. F. Haynes, P. Katz: The spectrum of vasculitis. Ann. Intern.

Med. 89: 660-676, 1978. The Leadership Award of the Columbus Citizens Foundation, Inc., for "Inspired Leadership and Outstanding Achievement in the Field of Medical Research," New York, NY October 8, 1988. American Association for the Advancement of Science/Westinghouse Award for Public Understanding of Science and Technology, 1988. The National Hemophilia Foundation Special Award for Research in AIDS, 1989. The Lee P. Brown National Public Service Award of 1989 presented by the National Academy of Public Administration and the National Society for Public Administration. The Duke University Award for Rheumatologic and Immunologic Research, 1989. The William Beaumont Award of the American Medical Association, 1989. The academic Excellence Award from Children's Hospital National Medical Center, Washington, DC, 1989. The Surgeon General's Exemplary Service Medal, 1989. The Surgeon General's Medallion, 1989. The 1989 Achievement Award of the American Association of Physicians for Human Rights. The 1989 National Medical Research Award of the National Health Council. The Flame of Hope Award of the Terri Gotthelf Lupus Research Institute, November 2, 1989. The 1989 Maxwell Finland Award in Infectious Disease presented by the National Foundation for Infectious Diseases. The 1989 Helen Hayes Award for Medical Research. Visiting Professor of Medicine at a large number of major medical schools throughout the country.

Publications:

Dr. Fauci has authored over 680 scientific publications in the field of basic and clinical immunology and infectious diseases.

Mr. Early. Mr. Chairman, I have to chair a meeting this afternoon that I previously agreed to at State-Commerce-Justice Subcommittee, and I want to thank you for letting Dr. Fauci put his statement on the record. I have numerous questions I will submit for the record, but I am disappointed that I cannot be here, because I think Dr. Fauci answers the questions very specifically more so than any of the other Directors, although they all answer them specifically.

Just one comment, Doctor. In your first chart, you say you take it to the bank. In banking, the more you put in, the more you get out, don't you?

Dr. Fauci. That is right.

Mr. Early. Mr. Chairman, thanks for letting me say that.

Mr. Natcher. Thank you, Dr. Fauci.

The committee will now recess until 2:00.

Dr. Fauci. Thank you, Mr. Chairman.

AIDS ALLOCATION

Mr. Natcher. Dr. Fauci, we are delighted to have you and your associates back again this afternoon. Since the 1990 appropriations bill did not specify the amount of AIDS funding for each institute, how did you allocate your total funding between AIDS and non-AIDS research?

Dr. Fauci. What we did, Mr. Chairman, is that we allocated the money according to the original budget submission. However, in accordance with the report language suggesting flexibility in the AIDS and the other than AIDS area, we expanded our definition of AIDS-related because we feel very strongly that there is some research in immunology and microbiology that by definition, even though the grant application doesn't contain the words HIV or AIDS in it, is critical to our understanding of the pathogenesis of HIV. So, although the original breakdown was according to our submission, we did exercise the flexibility that the committee suggested to us.

Mr. Natcher. Doctor, do you favor continuing this non-earmarking approach in 1991?

Dr. Fauci. I think it has worked well for us, Mr. Chairman, and I would be in favor of continuing as we did in 1990 where we have a general approach of the amount we would spend in our original submission, but have the option of being flexible as we execute the budget.

Mr. Natcher. What should be the rate of growth for AIDS research funding over the next several years, Doctor?

Dr. Fauci. Well, I think that the extraordinary rate of growth that we had in the earlier years almost out of necessity would begin to come down a little. We have gone, in our institute, from a 20 to 30 percent growth rate to now approximately 7.5 percent.

I think that the scientific opportunities are such that AIDS could still use an enhanced rate of growth, but as is always the case, given the constraints of the budget, if that is going to seriously impact on the other non-AIDS areas, we will have some concern about that. But the scientific opportunities are there to justify a substantial increase.

I can't give you a number. We have to see what the scientific opportunities are from year to year.

PEDIATRIC AIDS

Mr. NATCHER. Dr. Fauci, describe to the committee briefly where we stand in regard to pediatric AIDS and the efforts throughout NIH to find treatments for these young patients.

Dr. FAUCI. Mr. Chairman, we now have 47 AIDS clinical trial units which are a network of clinical trials programs throughout the country. We have 15 of them that have been specifically designated to do pediatric AIDS clinical trials, and several of the "adult" AIDS clinical trial units have a pediatric component so we have made a major effort over the last year or two to focus on the pediatric population, particularly with regard to clinical trials.

We have also been, I believe, significant players in the philosophical change that has occurred regarding clinical trials in pediatric populations. Prior to this past year, it was generally felt that not only should a drug not be approved for children, but it probably should not even be tested in infants and children until it has gone through extensive testing in adults.

We have seen over the past year a philosophical change where we do not have the time to wait for that, so we are now, for example in the ddI studies, doing simultaneous studies in children as we do them in adults.

I think this is an important advance and the right thing to do.

Mr. NATCHER. Have we made less progress on research relating to pediatric AIDS than on AIDS in adults, Doctor?

Dr. FAUCI. I would say that it has lagged somewhat, Mr. Chairman.

Pediatric AIDS and HIV infection in children have some significant differences from adult AIDS and HIV infection. Early on in the AIDS epidemic, when there were essentially no children with AIDS, much of the fundamental and clinical research was by necessity targeted to adults. When we began to see that children were infected to a great degree, then we shifted our attention appropriately to pediatric AIDS.

I would not say it is less in the sense of not as important, but I believe it has lagged. Hopefully in the next year it will catch up.

Mr. NATCHER. With only two thousand pediatric AIDS cases identified in the last nine years, is there a significant underreporting of these children, Dr. Fauci?

Dr. FAUCI. I think it is entirely underreporting in the sense of not realizing they are infected, but in diagnosis. The diagnostic criteria for AIDS in children are not as well defined and categorized as they are in adults, so we have many more children who are infected with HIV and who have had some deleterious conditions of that infection who might not necessarily be categorized, strictly speaking, as AIDS I think, therefore, that it is more the softness of the definition than underreporting.

But I must emphasize, Mr. Chairman, that we are going to see in the next several years a rather substantial burst of cases in pediatric populations because the new infections that are occurring now, particularly in the inner city minority groups, are such that we will be seeing many more pediatric patients than we have seen over the past years.

So the future does not bode very well for pediatric AIDS with regard to numbers.

MOUSE MODEL

Mr. NATCHER. Last year, you testified about the breakthrough of a mouse model for AIDS. Some scientists, are suggesting that this model may not work and may be even harmful. Dr. Fauci, is this a major set back?

Dr. FAUCI. No, I do not think it is a major set back. I believe what you are referring to, Mr. Chairman, is a recent report that if you, in tissue culture, infect a human cell with a mouse retrovirus and at the same time infect it with the human immunodeficiency virus, you can have a combining of the two viruses into a pseudo type that might *in vitro* be more virulent or more damaging to tissue culture cells than the HIV alone.

If you make an extrapolation into the mouse model and the model I told you about last year where we put the HIV into a combined immunodeficiency mouse that has had a reconstitution of their immune system, there is the theoretical possibility that an indigenous or natural retrovirus in the mouse might combine with the human virus leading to this more virulent strain.

It is a hypothetical possibility that we must be aware of, but the safety containment level that we use with mice that are infected with HIV is such that even if this did occur, it would not be of great consequence provided those containment facilities are constructed according to the recommended guidelines.

AIDS CLINICAL TRIALS

Mr. NATCHER. How has the demographic population of the AIDS clinical trials changed since the beginning of the community-based trials, Doctor?

Dr. FAUCI. Well, we have had what I see as significant changes even before the execution of the community-based trials. We have now funded our 18 community-based trials, but they are still in the process of getting the actual patient population into clinical trials. What has happened even before that, however, is that we have seen an improvement in the relative proportions of blacks, hispanics, and women in the clinical trial process.

Last year when we reported on this, it was about half of what it is now. We now have about 11 percent blacks and 11 percent hispanics, and there was somewhere around 6 or 7 percent of each last year. So the demography of pediatrics, minorities, and women is improving, but it still need to go a lot further.

RESEARCH CENTERS

Mr. NATCHER. Only a small share of your research funding, as you know, goes to centers, and you are not proposing any increase for them in 1991. Do you have concerns about the usefulness of the center mechanism, Dr. Fauci?

Dr. FAUCI. No, I do not, Mr. Chairman. The way we use centers, I believe it is good science and money well-spent. We have the vast majority of our resources in investigator initiated RO1's. We have a limited number of centers that we believe are doing a good job.

We do not believe that a major expansion of the center program would be in order.

INTRAMURAL RESEARCH

Mr. NATCHER. In-house research receives the largest rate of increase in your budget. Why is this your highest priority, Dr. Fauci?

Dr. FAUCI. Well, it is not our highest priority. We feel equally as strong about extramural as we do about intramural. If one compares the research project grants with intramural the percentages of the increases are 6.7 percent for the research project grants and 8 percent for intramural. But we have to take into account that there are no built-in increases in the intramural program where there are built-in automatic increases in the research project grant line.

So if we were to straight-line both of them, then the research project grants would even go up some because of the built-in increases while intramural would go down. So a 1 or 2 percentage point greater increase in intramural would keep it level with or more likely even a little bit less than the research project grant line. In essence what I am saying is that there really is no practical difference between the two, even though it looks like a couple of percent difference.

INCREASE IN GRANT APPLICATIONS

Mr. NATCHER. Your Institute has the highest growth rate in grant applications at NIH, as you know. Is this principally, Doctor, due to growing research interest in AIDS?

Dr. FAUCI. Certainly AIDS plays a role in that, but the area of fundamental immunology and microbiology is currently a very exciting area among young investigators, and we see at the fellow and medical school level a rather substantial proportion of people who get very interested in those areas, and I think it is a combination of that along with the extra interest in AIDS that accounts for the increase in numbers of applications.

GORGAS MEMORIAL LABORATORY

Mr. NATCHER. What is the status of the Gorgas Institute in Panama, and tell us, are these funds being recompeted in 1990?

Dr. FAUCI. The situation with Gorgas, Mr. Chairman, is that prior to last year there was a direct pass-through to fund the Gorgas Memorial Laboratory that was originally through the Fogarty International Center, but had been passed on to NIAID.

With the transfer was a requirement that it should no longer be an automatic pass-through, but should be competed, and not necessarily to support a laboratory in Panama. Based on those guidelines, we advertised for competition for these funds and gave the opportunity to Gorgas to compete. Since the RFA for that competition was at a period of time when it would not have been enough time for Gorgas to put in an application, we elected to fund Gorgas through a unsolicited but peer reviewed award through that transition period and that then gave them the option of coming in to compete for a regular research grant award in FY 1991.

Gorgas elected not to submit an application. We, in fact, got a good response to that RFA with receipt of a number of good applications. We intend to fund one or more of the most worthy applicaitons.

Mr. NATCHER. Mr. Conte, I yield.

Mr. CONTE. Thank you, Mr. Chairman.

Dr. Fauci, it is indeed a great honor for me to welcome you before our committee today. Your can-do spirit is infectious, no pun intended, and has spurred your doctors and scientists to do their very best work.

Chairman Natcher and I, along with the rest of this committee, are impressed by what you have done, and in the coming year we expect more good news out of your shop, and we wish you well. Keep up the good work.

Dr. FAUCI. Thank you, Mr. Conte.

IMPACT OF AIDS ON OTHER RESEARCH PROGRAMS

Mr. CONTE. Dr. Fauci, we realize that AIDS has become a major responsibility of your Institute.

You are also responsible for a large number of other infectious diseases. Have you been able to maintain your level of support for these other important areas through the years with increasing commitment to AIDS research?

Dr. FAUCI. We have been able to maintain support for areas of importance in other infectious diseases. However, it is very clear to us that the scientific opportunities in those other areas of infectious diseases have outstripped the resources at hand, so there certainly is more that we could do, and we would like to do more.

Mr. CONTE. Could you describe some of the ways of research on AIDS will contribute to the better understanding of other areas?

Dr. FAUCI. Well, as you know Mr. Conte, AIDS or HIV disease is a viral infection of the immune system, and from the basic research that has gone on in the area of AIDS research, we have learned an enormous amount about the regulation of the immune system, about how the immune system protects you, about how the immune system responds to pathogens and about how various regulatory genes of viruses have impacted on the body's immune system and other cellular functions.

I think the yield we are seeing in our understanding of all diseases that have an immunological component, as well as our ability now to target anti-viral agents to a particular function of a virus has received a tremendous shot in the arm from our work with AIDS and HIV. I think it is very much analogous to the situation years ago during the war on cancer in which money was put into cancer research with and the spinoffs in immunology, virology, etcetera, having been enormous.

We are already starting to see some of those spinoffs from AIDS research. One of the things that I pointed out in my presentation this morning was the growth and interest in utilization of the polymerase chain reaction that was spurred on with AIDS research aimed at looking for the AIDS virus and has now spun off as a diagnostic tool to detect very minute amounts of the Lyme Disease microorganism. So now we have a very important diagnostic test for Lyme Disease that was a natural spinoff from the work that was done with HIV. I could go on and on.

But broadly speaking, anything that has to do with an understanding of the immune system, autoimmune diseases, immunodeficiency diseases, as well as anything that has to do with understanding how microbes work, has benefited from HIV research.

AWARD RATES

Mr. CONTE. Very good. Out of the approved grant applications you receive, what percent will you be able to found under the President's budget?

Dr. FAUCI. Under the President's budget we will be able to fund 24.4 percent of approved grants in FY 1991.

Mr. CONTE. In your professional opinion what percentage do you think would be necessary to sustain high quality research?

Dr. FAUCI. Well, we have taken that question very seriously, Mr. Conte, and have looked at our portfolio of grant applications. We feel that there is very good science, easily worthy of funding at about the 45 percent award rate, so we think that if we funded 45 to 50 percent of approved grant applications we would still be funding excellent science.

So our award rate of 24 percent is almost half of what we think it should be.

HIV-2

Mr. CONTE. Doctor, HIV-2 is the AIDS virus that has spread in Africa, while HIV-1 is a predominant type in America. What is the difference between these two HIV types?

Dr. FAUCI. Well, the difference is at the protein level. You have differences in the amino acid sequences of the proteins of the different viruses. If you look at the nucleotide of the proteins, you have base pair differences.

It is really a matter of the difference in the genome. When you get a difference that is over a certain percent, you consider it a different virus. HIV-2 has significant enough difference in its envelope, the coat of the virus from HIV-1 that it is beyond the level and the scope of it being just a variant of the same virus. We, therefore call it a different virus.

HIV-2 also causes immunodeficiency disease. It infects the same type of cells. It is quite analogous to HIV-1. In fact, although we do not have much experience with HIV-2, there are investigators in West Africa who do have significant experience and tend to consider it to be somewhat less pathogenic than HIV-1, but the way it renders its harmful effects on the body are strikingly similar to HIV-1.

Mr. CONTE. There have only been, I am told, isolated cases of HIV-2 reported in the United States. Should HIV-2 become widespread here, are there any clincal or treatment implications and would we need different drugs to treat it?

Dr. FAUCI. The preliminary studies which have looked at the effect of the nucleotide derivatives, the kind of antivirals that AZT falls under, in an *in vitro* setting, show that the HIV-2 strains are sensitive to these nucleoside derivatives. It is likely that if HIV-2 becomes a problem here that it would respond to the same antiretroviral agents as the HIV-1 does.

Mr. CONTE. Should we be concerned about HIV-2?

Dr. FAUCI. Well, I think we always must be concerned about any emerging microorganism. As I mentioned in my formal discussion this morning, there are emerging microorganisms that we constantly have to stay on guard for. Certainly, HIV-2 could become a significant problem as the result of people coming to the United States and infecting others. There have been a couple of reports of infections in the United States in people who got infected in West Africa. We know that in Brazil, for example, which geographically shows some proximity to West Africa, there are significant numbers of cases. Also, in Western Europe where there is a lot more migration back and forth between West Africa and Western Europe, there are a significant number of cases.

I would not be surprised, since this is such a small world vis-a-vis travel, that we will start seeing cases that de novo arise here in the United States. Therefore, I believe we must be on the alert for it, and we cannot take it lightly.

DIDEOXYINOSINE (ddI)

Mr. CONTE. Doctor, as you well know, there has been great concern over the death rates in patients who are taking ddI through the expanded access program. According to the press, the mortality rate of patients in the community is ten times those who are taking the drug in a standard test.

What is going on here? Do you have any suggestions as to how we might improve access and preserve safety?

Dr. FAUCI. I think that the implication in the articles that you are referring to, Mr. Conte, that something is really going wrong is premature and there is no basis yet to make that conclusion. We need to look at the profiles of the patients that get on to the expanded access and I do not have the data yet. We are getting that data from the company. Preliminary discussions indicate that the people who died were so far advanced in their disease that it is very likely that their deaths had absolutely nothing at all to do with the drug but had to do with the fact that by the time they got on the expanded access, they were so sick they were going to die anyway.

In fact, there were a significant number of people who were on expanded access who actually died before they even got the first dose of the drug. However, if you were to read the paper, you might get the impression that it was the drug that caused it. That is something that is not only not established, but I doubt very seriously if it has anything at all to do with the drug.

Again, I will reserve any definitive statement until I see the data, but I would be willing to wage you a bet that it has to do with the advanced state of the disease and not at all to do with the drug.

MYCOPLASMA

Mr. CONTE. Well, that is encouraging to hear that. Encouraging that it may not be the drug. Doctor, an investigator over at Armed Forces Institute of Pathology found an interesting microbe called mycoplasma associated with AIDS infections.

Can you tell us what is the significance of this discovery?

Dr. FAUCI. I think it is safe to say, Mr. Conte, that we do not know yet what the significance of it is. Sometimes information on an observation like this gets either exaggerated in the press or reported in a way that might not be entirely accurate. This agent certainly is not the ideologic agent of AIDS.

It is a microorganism which they call *mycoplasma incognitum,* an organism that we have not seen before. At best, it is an opportunistic infection that had been isolated in many individuals with HIV infection. In fact, the NIAID held a conference in which we brought investigators together to look at the available data on this organism and we are trying as best we can with our available resources to help those investigators to straighten out just what it is. If it is an important opportunistic infection then perhaps a consideration should be given to treatment of that infection, for example, in a situation where an AIDS patient is deteriorating and you do not have any idea why. Its significance is not fully understood, but we are on top of it.

AIDS AND SEXUALLY TRANSMITTED DISEASES

Mr. CONTE. Transmission of AIDS is often intertwined with the spread of other sexually transmitted diseases, such as syphilis. What are we doing to look at the concurrent spread of AIDS and STD?

Dr. FAUCI. We have linked our work on STD very closely to our HIV effort. The point you make is a very important one. In fact, if you look at all the associations of various factors with HIV infection, the ones that in every study consistently show statistically significant associations or correlations are, one, genital ulceration and, two, syphilis. Because of that we have in our STD program, certain aspects of STD research which are considered directly HIV-related. This is another example of the situation to which I referred when the Chairman asked me about that flexibility of being able to use what we would call AIDS resources to study areas that are related to AIDS.

STD research, particularly in the areas of epidemiology and natural history of sexually transmitted diseases is very closely related to HIV research.

PERTUSSIS VACCINE

Mr. CONTE. I hear you folks developed a new vaccine for whooping cough. What are the advantages of this new acellular vaccine, and are you involved with the national vaccine program in developing this new vaccine.

Dr. FAUCI. Yes, we are, and we are represented on the National Vaccine Program. The vaccine you are referring to uses recombitant DNA technology to create a vaccine that lacks that toxic component of the whole pertussis bacteria that is responsible for many of the minor and major toxic side effects that children get when they get immunized with pertussis vaccine.

If this new vaccine turns out to be effective as well as safe, it will represent a way to prevent pertussis without having to worry about some of those dreadful complications that a very rare number of individuals get. While rare, they are nonetheless, devastating. Right now we have a number of these candidate acellular vaccines that are in phase one and phase two trials.

We are going to pick those that are the best, the top two or three, and advance them to phase two or three trials. We are, therefore, well into the clinical trial process in close association with the National Vaccine Program.

RAG-1

Mr. CONTE. Doctor, the master controller of the immune system, RAG-1 was discovered recently. What is the significance of this discovery and how will this help new AIDS research?

Dr. FAUCI. Well, what you are referring to is——

Mr. CONTE. RAG-1.

Dr. FAUCI. This is the molecular mechanism which accounts for the switching ability of a particular gene to code for a product that recognizes a wide variety of organisms. We have known for a long time that the immune system, with what looks like a limited armamentarium of genes is able to recognize a vast array of what we call antigens, for the practical purpose of infections. We will call them infectious disease antigens.

It has always been puzzling. We know that genes can rearrange in a way that would amplify their ability to recognize some different organisms. The exact mechanism of that has not been known until just recently in reports that have appeared literally over the past few months. So understanding that mechanism is giving us great insight into how the immune system can have a radar screen that can see so many different antigens.

CONTROLLING COSTS OF AIDS DRUGS

Mr. CONTE. Dr. Fauci, the cost of AZT is still way out in orbit, and it bothers me greatly. Very few can afford to pay for this drug, even with all of the price breaks, and uninsured people don't even stand a chance of paying for this drug. What is your Institute doing to help control the cost of AIDS-related drugs? Are you talking with the pharmaceutical industries to see what could help or how they could help about lowering the cost?

Dr. FAUCI. We cannot do anything directly, as I am sure you are aware, Mr. Conte, about controlling costs, but there are a couple of ways we can do it indirectly. One way is to get a couple more drugs out there that are as good as AZT, and that is what we are trying to do through our clinical trials process.

Once you do that, then good old American competition, I think, is going to bring the prices down. Secondly, through the Technology Transfer Act, when we now engage in a collaborative agreement with a biotechnology firm or a drug company for the development of a drug, we sign a collaborative research and development agreement, which contains a clause which says that we will have some say in what the price of that particular agent will be if it ever gets out on the market.

Mr. CONTE. Great.

Dr. FAUCI. So previously we would collaborate, but our hands would be tied and we would have no say in setting the ultimate price. Now, if we are going to put government resources and government energy into this process, we will have a say as to what is a reasonable price. I think that is the way we can indirectly have a positive impact on the price.

Mr. CONTE. That is great to hear. Thank you, Mr. Chairman.

Mr. NATCHER. Yes, Mr. Stokes, I yield to you.

Mr. STOKES. Thank you, Mr. Chairman.

MINORITIES AND AIDS

Dr. Fauci, it is nice to welcome you before our subcommittee again. In terms of the whole AIDS epidemic, give us a picture of the total amount of AIDS cases and then give us a picture of how minorities fit into that epidemic.

Dr. FAUCI. If one looks at the total number of AIDS cases in this country, we are approaching 120,000. Clearly, without question, minorities are disproportionately afflicted by HIV and AIDS. I can give you some quick numbers that I think will emphasize that.

If you look at the percent of the total population that is black, it is 11.7 percent. Twenty-seven percent of AIDS cases are among blacks. If you look at the percentage of the U.S. population that is Hispanic, it is 7.4 percent, yet 16 percent of our AIDS cases are among Hispanics. So the relative burden among minorities is extraordinary.

Mr. STOKES. In light of that fact, then, we talk about an extraordinary situation as it relates to minorities, what are we doing about it?

Dr. FAUCI. Well, we are doing several things, Mr. Stokes. We are trying to increase the minority participation in our clinical trials process and we have been somewhat successful. We need to do better, but the increases, I believe, have been substantial. For example, if one looks at the percentage of blacks that were in clinical trials sponsored by our Institute in 1987, it was 7 percent. We have doubled that in two years to 14 percent. The number of Hispanics has gone from 11 to 14 percent.

We pay particular attention to getting minority healthy black professionals, scientists, and clinical investigators involved in the process of HIV research, not only because we feel it is important for them, but also we feel that we can then have a better shot at getting the minority communities involved in clinical trials and at casting a wider net among the minorities.

I have provided for the committee members, on the dais there, two bits of information that you might find of interest. One is an NIAID Update, which indicates that we have recently funded—in fact I believe it was funded yesterday—an AIDS consortium center to combat AIDS among minorities. It is a consortium center grant at the level of $1,200,000. The total award is for $4,000,000 over a three-year period to the Association of Minority Health Professional Schools to help get them involved in AIDS-related research and ask some of the questions that we have been able in the past to ask in predominantly white populations. They will approach these questions in blacks.

That is one thing. The other thing is that we have developed a framework for action for improving ethnic and racial minority participation in AIDS research, and you have the plan in front of you here. So we are trying, and we recognize that we still have a way to go. We have met—I have personally met and my staff has met with a number of black community leaders, other minority leaders, minority scientists and clinical investigators to try and get them interested and involved in AIDS research as well as trying to get them to help us in getting minority communities involved.

I am sure you are aware, Mr. Stokes, of our community program for clinical research on AIDS. We made 18 awards for community clinical programs several months ago. By definition they are going to get at the grass-roots level of getting more minorities involved in the clinical research process, so all of these things are ongoing. Hopefully when I come back next year I will be able to give you even better numbers than I was able to give you today.

PEDIATRIC AIDS

Mr. STOKES. Okay. Now, in the same area, pediatric AIDS is a very special problem, too, in the minority community, is it not?

Dr. FAUCI. It is.

Mr. STOKES. Are we putting some money into the budget to try and attack this problem?

Dr. FAUCI. yes, we are. As I had mentioned just in the clinical trial process in pediatrics, we have about $37,000,000, and 15 of our 47 AIDS clinical trial units are specifically designated for pediatric clinical trials. A component of several of the other "adults" are also involved.

In addition since there are some differences in pathogenic manifestation among children, both in the area of neurological manifestations and due to the fact that the AIDS virus in an infant is attacking a developing immune system as opposed to a mature immune system. There are, therefore some different implications not only for immunological reconstitution, but also for therapy. These are the kinds of things that we are trying to approach from a basic science standpoint.

NEUROLOGICAL COMPLICATIONS OF AIDS

Mr. STOKES. I think you were present this morning when I asked Dr. Goldstein the question that he referred to you regarding the neurological complications of AIDS. Can you give us some information regarding that?

Dr. FAUCI. Yes. It is fascinating from both a basic scientific standpoint and from a clinical standpoint. In infants who get infected in utero or infected perinatally, the virus has a very devastating effect on their neurological development. We can see that very clearly.

In fact, if you compare the infant and the child to the adult, not only are the proportion of individuals that have neuropsychiatric abnormalities greater, but the intensity of the problems seems to be greater in the infant and the child. We believe that the reason for that is that you are dealing with a neurological system that is in the developmental process.

The interesting thing is, from studies that were done by Dr. Phil Pizzo in the National Cancer Institute, that when you treat children with AZT there is a more rapid reversal of the neurological abnormalities than is seen in adults that is a very important clue that indicates that there might not necessarily be direct viral damage to neurons, but there might be a metabolic process in which the virus infects a cell and the cell secretes a product that has a detrimental effect on neurological cells. We believe that at least some of those neurological abnormalities in the children are reversible.

That is very good news because if that is the case and if you treat them early and adequately, you may see a catching-up in their development.

We are hoping that that is the case, and that is the reason why in answer to the Chairman's previous question that I said it is absolutely essential to get those clinical trials going in children at the same time that you do them in adults. We must make a philosophical switch away from the concept that you can not do trials in a child unless all the T's have been crossed and the I's dotted in an adult, and I think we are moving towards that.

PEDIATRIC CLINICAL TRIALS

Mr. STOKES. Now, it was reported recently that there is at least one pediatric AIDS clinical trial underway that is placebo-controlled. I understand you feel the patients in the control group should receive AZT. Is that a correct statement?

Dr. FAUCI. That is.

Mr. STOKES. What is the status of that trial?

Dr. FAUCI. It is a trial supported by the Child Health Institute. We have had discussions with the Child Health Institute, and they have agreed that it will be a good idea in that trial to make available to people entering into the clinical trial the option of being on AZT if they want. That gets away from the previous criticism that there may be an individual who really has no other option but to get on a clinical trial with a placebo.

Now if someone wants to go on the clinical trial, they do have the option of getting AZT.

ASTHMA IN URBAN MINORITY POPULATIONS

Mr. STOKES. Now, Dr. Fauci, despite major advancements in the treatment of asthma over the past decade, we have witnessed an increase in its prevalence, especially among African Americans and Hispanic children in our inner cities.

Dr. Lenfant was here a few days ago, and he also mentioned this when he came before our committee. Can you give us your views on this?

Dr. FAUCI. Yes. I think it is a very serious problem. We are seeing it as you correctly mentioned, particularly in inner cities. We are seeing it in youngsters, and we are seeing it in elderly individuals, an increase in asthma morbidity and a very disturbing increase in mortality. On the basis of this, we have established an initiative that will be executed in fiscal year 1991 which we are calling the inner-city asthma program. This is a comprehensive two-phase intervention program to try and reduce this asthma-related morbidity for African American and Hispanic children residing in inner cities.

Another example of what we are trying to do with the resources that are already available is to increase the level of outreach and, therefore, asthma awareness in inner-city minority populations.

A good example is a program at UCLA. There is a large Hispanic community in southern California. We have a Center for Interdisciplinary Research in immunological disease at UCLA that has targeted asthma outreach efforts to the Hispanic community.

Mr. STOKES. Now, will you also be working with the Heart, Lung and Blood Institute on this?

Dr. FAUCI. Yes. Yes.

BONE MARROW TRANSPLANTATION

Mr. STOKES. Doctor, are we any closer to learning how to prevent the serious side effects of bone marrow transplantation?

Dr. FAUCI. Yes, we are. This is a very perplexing problem. It has been very much of an enigma to basic researchers for some time. But over the past year research on the ability to eliminate the reactive cells that are responsible for one of the great complications of bone marrow transplant, graft versus host disease, has proceeded such that we can now much more specifically eliminate these cells which interfere with the immuno-suppression that is necessary when you transplant an organ from one person to another when there is not an absolute match.

So things are moving along in that area, but it is a very difficult area of research.

Mr. STOKES. Is there any potential for this therapy for treating AIDS?

Dr. FAUCI. Yes, there is. As a matter of fact, Mr. Stokes, we have in the NIAID performed a series of bone marrow transplants between identical twins in which there was a well brother who had an HIV-infected brother and we transplant bone marrow as well as transfused lymphocytes from the well brother to the HIV-infected brother.

We did not see dramatic responses very likely because we had not adequately suppressed the HIV in the recipient. I think what we will probably be seeing, and that is one of the things that I hope for in the 1990's, that when we have a combination of drugs that can effectively suppress the virus so that you have virtually no new viral replication. In that case, we may be able to come in with either an identical twin or, since that is not very feasible for most people, a closely matched marrow, and be able to simultaneously suppress the virus and reconstitute the failed immune system.

So in our own armamentarium we look upon bone marrow transplant as a potential major way of attacking the HIV immunodeficiency.

Mr. STOKES. Thank you very much, Dr. Fauci. Thank you, Mr. Chairman.

Mr. **Natcher**. Dr. Fauci, we have a few additional questions.

Dr. Fauci, we want to thank you and your associates for appearing before our committee at this time in behalf of your budget request for the fiscal year 1991. It has been a good hearing, Doctor. As you have heard me say, together with Dr. Raub, that all the hearings with NIH are good as far as I am concerned, and that applies to all of the members of this subcommittee, because we are all concerned about it.

We are very much interested in it, and we appreciate having you appear at this time. Thank you very much.

Dr. **Fauci**. Thank you, Mr. Chairman.

[Questions and answers for the record and the justifications follow:]

Questions Submitted by the Subcommittee

AIDS VACCINES

Mr. Natcher. How many AIDS vaccines are currently in the human trial stage?

Dr. Fauci. There are currently ten clinical trials in which eight vaccines against the human immunodeficiency virus (HIV) worldwide are being tested. Six trials are underway exclusively in the U.S., one is ongoing in England and California, and the remaining are being studied in Zaire/France, Switzerland, and England.

AZT

Mr. Natcher. Recent studies recommended lower doses of AZT for AIDS patients. Do you expect any further drop in the suggested dosage?

Dr. Fauci. The NIAID has conducted a pilot study to determine whether a further dose reduction for AZT will be possible, and we are analyzing the information gained from this study to determine if an expanded study should be conducted. We are all encouraged by our earlier findings that a lower AZT dose is as beneficial to HIV-infected patients as the higher dose.

Mr. Natcher. How much does an annual supply of AZT cost at the current recommended dosage?

Dr. Fauci. The cost of AZT per year at the new dose level of 500 milligrams per day is approximately $250 per month per patient, or approximately $3,000 per year.

Mr. Natcher. Do you think Burroughs-Welcome will further lower the price of the drug?

Dr. Fauci. I have no information regarding any planned price reductions for AZT by Burroughs-Welcome.

Mr. Natcher. Can a high percentage of AIDS patients tolerate AZT?

Dr. Fauci. We expect that many more patients will be able to tolerate the drug at the reduced dosage level. However, it is still too early to tell how many more patients will be able to tolerate AZT therapy at the reduced level.

CLINICAL TRIALS

Mr. Natcher. How many new and continuing clinical trials are funded in your FY 1991 request, and how many of them are AIDS trials?

Dr. Fauci. We will not be funding any new clinical trials in FY 1991. However, we have 140 clinical trials continuing into FY 1991 of which 76 are AIDS clinical trials.

Mr. Natcher. How much funding does your budget include for clinical trials?

Dr. Fauci. We have budgeted a total of $157,761,000 for clinical trials in FY 1991.

TROPICAL DISEASES RESEARCH

Mr. Natcher. How much funding does your budget request for tropical diseases research?

Dr. Fauci. Our FY 1991 request for tropical disease research is $39,205,000.

Mr. Natcher. Given your Institute's commitments in other areas, can you continue to target this field as a major research focus?

Dr. Fauci. Recently tropical diseases have been emerging in various parts of the United States. With increases in world travel and the opening of international borders, it is imperative that we maintain our commitment in this area of research. Much of the tropical disease research funded by the NIAID is unsolicited investigator initiated research rather than NIAID targeted research.

SEXUALLY TRANSMITTED DISEASE RESEARCH CENTERS

Mr. Natcher. How many of your proposed Sexually Transmitted Disease Research Centers would you fund in FY 1991, and at what cost?

Dr. Fauci. We anticipate funding two to four Sexually Transmitted Disease Cooperative Research Centers in FY 1991 at an estimated cost of $4.1 million.

CHRONIC FATIGUE SYNDROME

Mr. Natcher. What is the current thinking on the infectiousness of chronic fatigue syndrome? How much FY 1991 research funding are you targeting for this disease?

Dr. Fauci. There is no scientific evidence that chronic fatigue syndrome is communicable. Nevertheless, patients often cite a "flu-like" illness as a precipitating factor. Thus, we can envision the possibility that an infectious agent will "trigger" the syndrome in susceptible individuals. The triggering agent might very well be different at different times and in different places. The situation is somewhat analogous to what may occur in diabetes; that is, an infectious agent may precipitate diabetes in genetically susceptible persons, but diabetes per se is not transmissible.

In FY 1991 we are estimating our chronic fatigue research funding at $1,595,000.

PEDIATRIC AIDS

Mr. Natcher. Your justification indicates that more infants are being born of mothers who acquired AIDS heterosexually rather than through I-V drug use. Isn't needle-sharing an easier way to contract AIDS than heterosexual contact?

Dr. Fauci. Needle-sharing does make it easier to transmit the virus than heterosexual contact. However, in this country, more babies are acquiring HIV infection from mothers who became infected with HIV by sexual partners who use intravenous drugs rather than through drug use on the part of the mother. This trend is recent and demonstrates the inseparable nature of intravenous drug use and heterosexual HIV transmission in the AIDS epidemic in the U.S.

AIDS RESEARCH CENTERS

Mr. Natcher. How much NIAID research project grant funding is received by principal investigators associated with the AIDS research centers?

Dr. Fauci. The principal investigators of our Centers for AIDS Research were awarded $11,621,000 in research project grants funding from NIAID in FY 1989.

AIDS

Mr. Natcher. What is the most recent estimate of the average incubation period between exposure to the AIDS virus and first evidence of being HIV positive?

Dr. Fauci. HIV infection follows a wide range of progression rates for reasons that are not fully known. Some people may experience a rapid deterioration in their immune system and develop full blown AIDS in a matter of a year or two, while others infected with HIV may remain asymptomatic, with intact immune systems, for a decade or more. Recent evidence from the Multicenter AIDS Cohort Study (MACS) found that strains of HIV isolated from MACS participants who have remained asymptomatic throughout their involvement in the study had a greatly reduced ability to infect other lymphocytes than strains of HIV taken from MACS participants who became infected with HIV and then progressed to AIDS during the relatively short time of their involvement with the study. In these laboratory studies, genetic analyses revealed a small difference in the DNA composition between the virus which were associated with a rapid progression to AIDS and those viruses found in persons who remained asymptomatic for long periods of time.

This scientific advance has the potential of at least partially answering the puzzling question as to the differences in the rapidity of disease progression in different individuals. This type of information may be highly useful in counseling a person as to his/her overall prognosis and in evaluating the effectiveness of different therapeutic interventions.

DISEASE FUNDING

Mr. Natcher. Provide an estimate of your Institute's spending on the following diseases for FYs 1989-1991. Lyme disease, asthma, and sexually transmitted diseases.

Dr. Fauci. In FY 1989 we spent $2,268,000 for lyme disease. In FY 1990 and FY 1991 we are estimating our funding levels at $3,554,000 and $3,747,000, respectively.

In FY 1989 we funded $5,630,000 in asthma research. In FY 1990 we are estimating our funding level at $6,099,000. In FY 1991 as a result of entering Phase II of an intervention program to reduce asthma-related morbidity for African American and Hispanic children residing in the inner city, we estimate our funding level to be $9,325,000 for asthma research.

In FY 1989 we spent $35,824,000 in STD research. In FY 1990 and FY 1991 we estimate our funding levels at $40,781,000 and $42,751,000, respectively.

HEPATITIS C

Mr. Conte. What work is being done in Hepatitis C research?

Dr. Fauci. This is an area of great interest to the NIAID given its mission to promote research on infectious agents as well as their prevention and therapy. However, at this stage hepatitis C research is limited. Information on the cloned viral genome and an antibody test have been available for less than a year. Because of this short time frame, the NIAID has not yet received any grant applications in this area. However, many investigators around the world are using the antibody test for research purposes. They are examining samples from various study populations to look for routes of transmission and to study the natural history of disease.

Samples supplied by our own intramural scientists along with those from a Clinical Center investigator were instrumental in determining that the antibody test works. The polymerase chain reaction is being used to look for the minute amounts of virus associated with infection and chronic disease. With these newly available and highly sensitive reagents intramural scientists detect viral replication very early after infection.

Mr. Conte. Are you looking at alpha interferon and other potential compounds that could be used to treat Hepatitis C?

Dr. Fauci. The New England Journal of Medicine recently published the results of two trials using alpha interferon to treat hepatitis C chronic carriers. One study was performed by the NIDDK intramural scientists and the other by a multi-center group sponsored by Schering Plough. Although promising responses occurred during therapy, the treatment regimen does not cure. Longer therapy trials may be warranted.

A small study about to be published evaluated Ribavirin -- a broad spectrum, licensed, oral, and well-tolerated antiviral. Responses similar to those with alpha interferon were noted. An efficacy trial expanding patient numbers and therapy time and using the recently developed tests to follow viral markers would be timely.

INTERNATIONAL AIDS

Mr. Conte. Doctor, the AIDS epidemic touches all parts of the globe. Over 140 countries have reported cases. The political and social effects of the world AIDS pandemic has a substantial impact here at home. What is your Institute doing abroad to help other scientists fight the disease?

Dr. Fauci. The NIAID supports a wide range of activities in the international arena through basic, epidemiologic, clinical, and vaccine research. As a result of these efforts, scientists in many countries are gaining invaluable experience in the conduct of research as well as benefiting from an ongoing information exchange.

Our international epidemiologic research studies are addressing the compelling scientific issues involved. These_studies include research of mother-infant transmission of HIV, heterosexual transmission, sexually transmitted diseases as co-factors of HIV infection, diarrheal diseases, and other urgent matters relevant to HIV infection in the U.S. and the Third World. The NIAID fosters international research through grant and contract awards directly to research institutions as well as staff consultations with the World Health Organization, participation at international meetings, and collaboration with other internationally active agencies of the U.S. Government such as the Centers for Disease Control and the Agency for International Development.

The NIAID is pursuing two main objectives in its international activities. 1) encouraging and supporting U.S. investigators in foreign-based studies of the natural history of HIV infection, the efficiency of different modes of HIV transmission, and the relative risk of different opportunistic infections, and 2) fostering the development of research skills and the administrative infrastructure in foreign institutions that may participate in future clinical trials of vaccine or potential AIDS therapies. At present, these activities are focused on research and institutional development in Africa, Latin American, and the Caribbean, where rates of heterosexual transmission and perinatal HIV transmission are very high. These populations can furnish a wealth of information on the heterosexual transmission of HIV. In addition, they may be more easily studied than similar populations in the U.S. because intravenous drug use is much less prevalent in these countries.

The NIAID also supports a contract with the Pan American Health Organization (PAHO), World Health Organization Regional Office for the Americas, to stimulate HIV research in Latin America and the Caribbean. Another international effort is Project SIDA, a series of epidemiologic, clinical, and laboratory science studies in Kinshasa, Zaire. These studies are co-sponsored by the Zairian Ministry of Health, the CDC, the Armed Forces Institute of Pathology, the Institute of Tropical Medicine in Antwerp, Belgium, and the NIAID.

The NIAID staff have begun contacts with investigators and research organizations in foreign countries to discuss the possibilities of conducting AIDS vaccines research. These preliminary international meetings will serve as a forum for the discussion of the most efficient ways to set up and run AIDS vaccine efficacy trials in developing areas, such as Africa where the incidence of HIV infection is high. The NIAID staff interact with three international organizations to discuss issues surrounding international AIDS vaccine clinical trials: the World Health Organization to discuss criteria for international vaccine clinical trials, the Medical Research Council of Great Britain regarding collaborative efforts in vaccine research and development, and the European Community AIDS Vaccine Program regarding issues of reagent exchange and technology transfer.

In basic research, the NIAID supports investigators outside the U.S. who are involved in the targeted discovery and development of potential AIDS therapies. These efforts include grant and contract awards for basic research as well as other associations with scientists and organizations around the world, such as consultations with the World Health Organization on matters related to the discovery and development of therapies for HIV-infected people, exchange of information at annual meetings with participants in the AIDS Directed Program, Medical Research Council of Great Britain, and participation in meetings with the National Institute of Biological and Safety Controls in Great Britain.

Mr. Conte. Have you gained useful knowledge from your foreign counterparts?

Dr. Fauci. Certainly. This wide variety of activities has created a vital information and resource exchange, which has fostered the establishment of international collaborative networks that are critical to countering a disease that has reached epidemic proportions in many areas of the world.

Mr. Conte. Tell me more about your International Collaboration in AIDS Research (ICARs) program.

Dr. Fauci. The International Collaboration in AIDS Research (ICARs) is a key component of the NIAID international AIDS effort. The ICARs are grants made to American universities to foster institutional relationships and undertake epidemiologic studies with investigators in foreign countries. Awards have been made for collaborative research in Uganda, Mexico, Brazil, Malawi, and Zaire. These grants seek to build institutional research capabilities in developing countries. The training for foreign nationals in HIV research is an integral mission of the ICARs. Components of all ICAR grants are looking at factors related to heterosexual and/or perinatal transmission of HIV.

AIDS VACCINE

Mr. Conte. Your Institute has been taking the lead in developing an AIDS vaccine in monkeys. What obstacles do you face in creating a vaccine for humans?

Dr. Fauci. There are three areas that we are working especially diligently on to further our chances of developing an effective AIDS vaccine. The first is the issue of the genetic variation of the virus. Studies that explore the biologic consequences of HIV genetic variation in terms of vaccine development are important because the production of a vaccine for AIDS is made much more difficult by the frequency with which HIV mutates. These mutations can result in subtle but significant changes in viral structure, which could render a vaccine ineffective. Investigation into the rate and extent of viral genetic mutation will provide scientists with critical knowledge needed for developing an effective AIDS vaccine.

The second is the area of adjuvant development. A subunit vaccine which utilizes a killed portion of a virus or bacteria is likely to be the ideal candidate for a clinical trial. Thus, an effective adjuvant, or a compound that enhances the immune response to a vaccine, may be highly important.

The third area includes basic immunological issues, such as identifying the components of the immune response needed for an effective vaccine. This issue is vital because HIV seems to require a more complex immune response than the production of antibodies, the basis of all existing vaccines.

Mr. Conte. Do you have other vaccine candidates in the works?

Dr. Fauci: We hope to have two additional vaccines in clinical trial by the end of 1990. In addition, there are many candidate vaccines at all stages of preclinical development. These include extensive experiments in animal models with whole inactivated virus vaccines.

PCR TECHNIQUE

Mr. Conte: I have been hearing a lot about the PCR reaction. Your Institute has been instrumental in developing a better test for Lyme Disease with this technique. How would the test for Lyme Disease work?

Dr. Fauci: The critical requirement for the PCR test to work is the presence of at least one Borrelia burgdorferi cell in the clinical specimen. If one is present, the PCR test possesses the potential to detect the borrelia. The basis of this test revolves around identification of a genetic sequence unique to B. burgdorferi. Then we manufacture DNA probes that can bind only to that sequence and we use an enzyme reaction that will cause that sequence to be amplified a thousand times or more if the probes find that sequence.

The PCR has applications to many different diseases. In each case the process is essentially the same. The difference is that in each case a probe specific to the disease in question will be used.

Mr. Conte: What are the potential uses of PCR in AIDS research?

Dr. Fauci: Sensitive methods are needed to detect the human immunodeficiency virus (HIV) in body fluids as well as the genetic material of the virus that becomes integrated into the DNA of infected cells. The ability to detect virus with a high degree of accuracy is especially important because, after infection, HIV often becomes latent, producing few viral proteins. During this latency period, currently used methods of detecting viral proteins or antibodies to HIV in body fluids can produce false negative results. This situation may result in a "window" of time during which HIV-infected people may test negative for HIV yet still be infected and capable of transmitting the virus.

Polymerase chain reaction (PCR) is a recently developed laboratory technique for generating large amounts of genetic material that may be present in limited quantity and therefore difficult to detect by other techniques. Because PCR detects the genetic material of the virus rather than proteins associated with infection, it offers a sensitive method to determine infection even if the virus is latent and producing no viral proteins.

Studies using PCR involve several scientific areas relevant to HIV infection, including clinical trials, basic research, and epidemiologic studies. Clinicians could benefit from this highly sensitive method by using it to detect the presence of HIV, to correlate the expression of HIV genes with clinical observations, and to measure the effectiveness of anti-HIV drugs. Using PCR has made it possible to identify genetic sequences of HIV in infected people up to three years before their tests results are positive using antibody assays. It has also helped to identify HIV-infected infants born to infected mothers. Furthermore, PCR can be used to examine the expression of HIV genes during the course of infection and to monitor changes in the HIV genome in infected people as the virus progresses from latent to virulent stages.

The NIAID has initiated a development program to evaluate and standardize PCR amplification and to detect HIV in both research and clinical laboratories. For clinical research, the NIAID sponsors a coordinated effort called the PCR Standardization Groups. These groups are attempting to extend the use of PCR into clinical settings by determining whether the technique can be used to detect HIV infection in patients. The PCR is still under development for clinical use. The transfer of PCR technology to clinical laboratories requires the coupling of PCR amplification to sophisticated detection technology to enable a high-capacity, automated operation.

For basic research, PCR affords an excellent opportunity to measure the ability of antiviral drugs to block expression of HIV genes, sequence regions of the HIV genome, and perform studies of genetic variation.

NATIONAL COOPERATIVE DRUG DISCOVERY GROUPS

Mr. Conte: How do your AIDS drug discovery groups go about selecting a potential medication for testing against AIDS?

Dr. Fauci: The core of the NIAID drug discovery effort is a network of collaborative groups, the National Cooperative Drug Discovery Groups (NCDDGs), which bring together expertise from industry, academia, and government.

When the NCDDG researchers identify compounds that show promise in vitro, the drug discovery part of the process, the next step involves studies in appropriate animal models. This step begins the preclinical phase of the drug development aspect of bringing a drug from the laboratory into clinical trial. The NIAID sponsors research to test compounds identified as potential drug candidates using random screening or targeted drug discovery.

The animal studies establish toxicology, potential dose levels, and pharmacokinetics of the drug. If the results of animal testing are favorable, the compound becomes a candidate for clinical trial. Significant headway in AIDS drug development has been made through the NCDDGs. This year, four new antiretrovirals entered phase I clinical trials: dideoxyinosine (ddI), N-butyl DNJ, soluble CD4, and dideoxydidehydrothymidine (D4T); two of these, soluble CD4 and D4T, were developed by the NCDDGs; the others were existing drugs.

Mr. Conte: Do you work with the pharmaceutical industry in coming up with some candidate compounds?

Dr. Fauci: We established the NCDDGs to address the problem that many research institutions lack the critical combination of scientific talents and resources needed to translate leads from basic research into new AIDS therapies. The cooperative agreement mechanism through which the Groups are funded permits an optimal combination of research expertise from diverse institutions and industries, including pharmaceutical companies. This program concentrates its resources on basic research, whereas the cost of the later phases of preclinical drug development is placed in the private sector.

Many private pharmaceutical companies participate in this program. These companies gain valuable knowledge in basic science. In return, industry's experience in drug development expedites the preclinical studies needed to move drugs to clinical trial. In addition, we work extensively with the pharmaceutical industry in clinical trials design and execution.

CENTERS FOR AIDS RESEARCH

Mr. Conte: You have started Centers for AIDS Research at several universities. These grants are targeted for investigators with outstanding track records in AIDS research. How will the Centers program contribute to better research?

Dr. Fauci: The Centers for AIDS Research (CFAR) program promotes the development of new scientific knowledge about HIV infection, with the ultimate goal of improving the diagnosis, treatment, and prevention of AIDS. The CFAR program is unique in that the award is a core support grant intended for groups of established investigators conducting AIDS and AIDS-related research that is already funded by the NIAID and other Institutes of the NIH.

The CFAR award supports activities that consolidate and focus AIDS research into a coordinated administrative and scientific structure. A typical CFAR award supports several core laboratory or analytical facilities, provides developmental funds to recruit new investigators into the Center, and provides support for administration, planning, and evaluation. Funds may also be requested for alterations and renovations to upgrade laboratories and provide proper containment facilities for work with HIV and related retroviruses.

The directors of the CFARs are expected to provide strong leadership in facilitating creative, interactive AIDS research activities among a variety of laboratory and clinical investigators. Each CFAR is a major element in the organizational structure of the institution receiving the grant.

Mr. Conte: In your professional opinion, how many centers do you think are necessary to do an optimal job?

Dr. Fauci: The NIAID has established eleven CFARs during the past year and a half. We believe that the national AIDS research effort would benefit greatly if we could establish an additional five to six CFARs in appropriate institutions.

GENETIC SEQUENCING

Mr. Conte: You are working very hard in the field of gene sequencing. How does a gene database help you in AIDS research?

Dr. Fauci: A gene database could help address, in the future, one of the big issues we now face in dealing with the AIDS viruses, and that is, the strain variations. Right now some of the questions we must answer include: 1) How many strains does a patient have at one time? 2) Do different strains attack different tissues and cells? 3) How do different strains affect the progression of AIDS in patients? A gene database could help correlate the genetic sequences of various strains of AIDS viruses.

Mr. Conte: Are you working with the new Center for Human Genome Research?

Dr. Fauci: Yes. The NIAID enthusiastically supports the Human Genome Research Center. Many of the NIAID's initiatives concern the genetics of the immune response and this remains integral in the efforts of understanding the human genome. The NIAID holds an advisory position on the NIH Human Genome Center Coordinating Committee. This is an NIH interagency committee established to assist the NIH Office of Human Genome Research by providing for the exchange of information, establishing research goals and facilitating joint sponsorship of specific projects.

BASIC RESEARCH ON AIDS

Mr. Conte: Solid basic research in virology and immunology holds the key for breakthroughs, not only for AIDS but for other diseases as well. Tell us what your Program of Excellence in Basic AIDS Research is all about.

Dr. Fauci: The Program of Excellence in Basic Research on AIDS (PEBRA) was begun very early in the AIDS effort to develop a multidisciplinary mechanism for basic research relevant to HIV infection. These large grants enable scientists in diverse fields of research to address questions on the pathogenesis of AIDS and related opportunistic infections by using approaches from immunology, virology, and cell and molecular biology. We will be evaluating the progress of these programs carefully over the next few years. In effect, the concept underlying the PEBRAs has been improved upon and revamped into the CFARs. Thus, the CFAR project has become the chief center mechanism for basic research of HIV disease.

Mr. Conte: How do these grants differ from the traditional R.O.1. grants?

Dr. Fauci: The PEBRA grants are program project grants (P01). Program project grants generally involve the organized efforts of relatively large groups, the members of which are usually under the leadership of an established investigator.

AIDS OUTREACH & TECHNOLOGY TRANSFER

Mr. Conte: Dr. Fauci, you sponsor an AIDS Outreach and Technology Transfer Program. What activities are involved in your outreach program?

Dr. Fauci: An important part of the NIAID's mission is to convey as quickly as possible to health professionals and to the public the results of its many research programs. In particular, the NIAID recognizes the need for intensive, targeted outreach to relevant health professional communities to ensure that new research information regarding AIDS is translated rapidly into care of AIDS and ARC patients. A major outreach effort of the Institute to minority health professionals and to all health professionals who work with minority populations.

The NIAID has sponsored more than a dozen workshops and conferences to provide researchers, health care providers, and educators with information on AIDS that targeted either a special population, such as minority physicians, or a particular issue, such as the importance of clinical trials. One conference was held to establish and communicate state-of-the-art recommendations for the treatment of pneumocystis carinii pneumonia, a major killer of persons with AIDS. Other conferences provided a forum for the Institute to communicate directly with constituents on important issues.

In order to assist physicians and patients to find appropriate clinical trials, the NIAID, with the cooperation of the Centers for Disease Control, established the AIDS Clinical Trials Information Service (1-800-TRIALS-A). The service includes information on all federally sponsored clinical trials of AIDS drugs in the U.S. Trained bi-lingual specialists (English/Spanish) answer questions by referring to an extensive computer database. A written copy of the information requested can also be sent to the caller. In addition, the information is now available on databases through the National Library of Medicine.

A new NIAID publication, "AIDS Clinical Trials: Talking It Over," was written and produced in both English and Spanish. It is intended for doctors to give to their patients to help them understand what trials are and decide whether or not to participate.

Mr. Conte: Tell us more about the technology transfer program. Who benefits from the program?

Dr. Fauci: The NIAID AIDS Outreach and Technology Transfer Program is intertwined. Through the use of workshops and publications, we provide the latest scientific information to the biomedical research community.

NIH AIDS REAGENT REPOSITORY

Mr. Conte: AIDS research often requires hard-to-obtain chemical agents. You got going an AIDS reagent repository to facilitate the supply or rare compounds. How does this program work?

Dr. Fauci: The NIAID AIDS Research and Reference Reagent Program (Repository), designated as one of three World Health Organization AIDS Reagent Centers, facilitates the exchange of reagents needed for biochemical research on AIDS and related retroviruses. The Repository distributes samples of cells, clones, virus isolates, and antibodies worldwide to investigators whose research relates to infection by AIDS. Further, the Repository encourages collaborative research aimed at the standardization of reagents and laboratory techniques.

The Repository relies on donations of reagents from individual laboratories and companies. Scientists are encouraged to contribute to the Repository. In some cases, small samples provided by investigators are expanded by the NIAID contractors before the reagent is available through the Repository. Information concerning the identification, purity, and activity of the reagents are provided by the donors. Contributors to the Repository are cited in the reagent catalog as the source and are acknowledged in publications by the recipient. Contributors also receive quarterly reports on requests for their reagents. Scientists who do not wish to contribute reagents are often amenable to being listed as willing to consider collaborative efforts.

Repository catalogs are published approximately every six months. These catalogues contain descriptions of reagents, contributors, and reference publications, as well as biological safety information, vendors of AIDS research reagents, scientists willing to consider collaborative efforts, and all forms necessary to receive and contribute reagents. Updates to the catalog are sent periodically to inform the scientific community when requested reagents have been obtained. Future catalogs and updates will contain protocol information as well.

Mr. Conte: Are these compounds going out for commercial purposes?

Dr. Fauci: The reagents within the repository are made available to researchers in a wide range of organizations, including commercial enterprises. In return, many organizations also contribute to the repository. Many of these reagents, such as viral strains of HIV, are critical to the development of new commercial products. However, the repository itself is not involved in the commercialization of its reagents. Furthermore, it supplies reagents only for research and not for commercial production.

PEDIATRIC AIDS

Mr. Stokes: Please give us an update on pediatric AIDS. What progress is being made in this area?

Dr. Fauci: The AIDS epidemic has hit minority children particularly hard with eighty-nine percent of the pediatric AIDS patients being African American or Hispanic. To address their special needs, we have increased the number of pediatric AIDS clinical trials units receiving funding to 15 enabling researchers to begin phase II and III trials in children. A new initiative will be published in the near future that will further expand our efforts to reach HIV-infected children and pregnant women; awards are expected to be made in the Fall of 1990. We have also strongly encouraged the units that accrue primarily adults to begin pediatric studies as well. As a result, several have begun these vital studies. Another important component to the expansion of pediatric trials units is the establishment of perinatal centers serving women in at-risk populations. This feature will provide for increased attention given to pregnant HIV-infected women and their children in AIDS clinical trials.

Through these efforts, we achieved a major advance in pediatric AIDS this year. Our studies contributed to the recent FDA award of treatment IND status to AZT for children three months to 12 years of age who have AIDS or symptoms of HIV infection. This important advance will make AZT the first treatment for HIV infection to become widely available for children, furnishing hope of improving or even extending their lives.

A critical goal of AIDS treatment research is to halt the transmission of HIV from an infected mother to her baby. The ACTG is sponsoring several studies using AZT in both newborns and pregnant women to try to block this form of HIV transmission. This studies are now getting underway. We have begun the first clinical trial of AZT in pregnant women, a vital first step toward determining whether zidovudine given during pregnancy can prevent mother-to-baby transmission of HIV.

Several major epidemiologic studies are researching questions of transmission of HIV infection from mother to child. One such study, Cohort Studies of Perinatal Transmission of HIV and Related Retroviral Infection, looks at the mechanisms and cofactors of perinatal HIV transmission. This multicenter, prospective study is also looking at the effect of pregnancy on the natural history of HIV infection and the natural history of HIV infection in the infants born to HIV-infected women.

Two other studies are also researching these critical issues. The Women and Infants Transmission Study (WITS) is a collaborative, multicenter study at four sites in New York, Chicago, Boston, and Puerto Rico which will recruit approximately 700 infected women. A pilot study phase is currently underway. A second study, Maternal Factors Influencing Perinatal Transmission of HIV, addresses the natural history of pregnancies in infected and uninfected women with HIV, both drug and nondrug users. This study will be conducted at the University of Medicine and Dentistry of New Jersey. A pilot study phase is currently underway.

Studies in basic science are also increasing knowledge of the mother-to-child transmission of HIV. Scientists have developed a mouse model of a retrovirus that produces an AIDS-like disease in small animals. Infected mothers can transmit disease to their offspring during birth and nursing. Drugs are being tested in this model for efficacy against these forms of retroviral transmission. Investigators have also developed a heterosexual transmission model for simian immunodeficiency virus (SIV) infection. This model, used to study potential drugs that may prevent transmission, has already given us insights into heterosexual retroviral transmission.

Mr. Stokes: What amount of resources is being put into this area in FY 1990? What portion of the AIDS budget does this represent? What would the FY 1991 level be under the President's budget?

Dr. Fauci. The NIAID is spending approximately $34 million in pediatric AIDS research in FY 1990. This figure represents about 8 percent of the Institute's AIDS budget. For FY 1991, the level in the President's Budget would be approximately $35.7 million or approximately 8 percent of the AIDS budget.

Mr. Stokes. In your professional judgement, do you think that this amount is sufficient for pediatric AIDS?

Dr. Fauci. I believe that the relative proportion of our resources devoted to pediatric AIDS is appropriate. However, if additional resources were provided to the NIAID, the scientific opportunities exist for us to productively utilize the funds in Pediatric Aids research.

AIDS VACCINE

Mr. Stokes. Earlier, you shared with us your optimism about the possibility of an AIDS vaccine. How far away is this? How soon Might we see an~~d~~ AIDS vaccine?

Dr. Fauci. Scientists developing a vaccine for HIV infection must complete additional studies in animals. This research is necessary to develop an understanding of how these exciting potential vaccines protect test animals from becoming infected with organisms that are highly similar to HIV. These studies are critical to the translation of results in animal research to a product that will be safe and efficacious in people. Then, much work remains in testing a candidate vaccine in people, including phase I, II, and III clinical trials, each which will take several years to complete. It is conceivable that a vaccine would be generally available within this decade.

CHRONIC FATIGUE SYNDROME

Mr. Stokes. How much support is going toward research directly related to chronic fatigue syndrome? How many grants and contracts does this include? What would be the level in FY 1991 under the President's budget?

Dr. Fauci. The NIAID will spend $1,531,000 in FY 1990 for research directly related to Chronic Fatigue Syndrome. This level of funding will support approximately three grants and one intramural project. In the FY 1991 President's budget request, we estimate that $1,595,000 will be expended for Chronic Fatigue Syndrome research.

Mr. Stokes. Are you trying to stimulate research in this area?

Dr. Fauci. Yes, we are stimulating grant applications by using a Program Announcement and by talking with potential investigators, providing them with information and application forms. Of perhaps greater importance at this time are the efforts being made by both extramural and intramural staff to bring investigators together in collaborative efforts to confirm results or follow-up on new leads.

LYME DISEASE

Mr. Stokes. I understand that your Institute was responsible for developing a new technique to enable the effective diagnosis of Lyme Disease. How does this new technique differ from current diagnostic methodologies?

Dr. Fauci. Current methodologies depend on the detection of a serological response in the patient of components of B. burgdorferi. The tests depend upon the detection of antigen-antibody responses. The sensitivity and specificity of tests that detect these reactions are not great enough for those cases in which the patient has a minimal or low serological response to B. burgdorferi. The PCR test on the other hand is based upon detecting genetic material that is unique to B. burgdorferi and it has the potential to detect the presence of only a single borrelia in a diagnostic sample. Thus this test is much more specific and sensitive than currently available methodologies.

NEW AND COMPETING RESEARCH GRANTS

Mr. Early. Dr. Fauci, how many new and competing research grants will the NIAID fund under the proposed budget request, and how does this compare to FY 1990 and FY 1989?

Dr. Fauci. Under the proposed budget request, approximately 580 new and competing research grants will be funded by the NIAID. In FY 1989, 652 new and competing research grants were funded, and approximately 476 will be funded in FY 1990.

PAYLINE PERCENTILE

Mr. Early. To what payline percentile would you fund under the FY 1991 request?

Dr. Fauci. In FY 1991, the NIAID will be funding research project grants up to the 19.0 percentile.

Mr. Early. How does this compare to FY 1990 and 1989?

Dr. Fauci. In FY 1990, we will be funding research project grants up to the 19.0 percentile, compared to the 20.0 percentile in FY 1989.

Mr. Early. What would the payline percentile be, exclusive of the AIDS grants?

Dr. Fauci. The payline percentile for AIDS is the same as for non-AIDS grants. For FY 1990, the percentile is projected to be 19.0 as compared to the 20.0 percentile in FY 1989.

PRIORITY SCORES

Mr. Early. Can you give us an estimate of what the priority scores are?

Dr. Fauci. The average priority score at the 19.0 percentile is approximately 130. However, I must point out that there is no valid correlation between a priority score and a percentile since the NIAID uses percentiles and not priority scores as the main measure of scientific merit.

AWARD RATES

Mr. Early. What percentage of approved grants would be funded and how does this compare to the past two years?

Dr. Fauci. In FY 1991, 24.4 percent of approved grants would be funded, compared to 31.9 percent and 22.0 percent in FY 1989 and FY 1990, respectively.

Mr. Early. What is the breakdown between non-AIDS and AIDS?

Dr. Fauci. For AIDS, the award rates for FY 1989, FY 1990, and FY 1991 are 39.8, 27.0, and 21.3 percent, respectively. For non-Aids, the award rates for FY 1989, FY 1990, and FY 1991 are 29.6, 19.9, and 25.9 percent, respectively.

Mr. Early. With the exception of FY 1990, haven't award rates been significantly higher in the past?

Dr. Fauci. With the exception of FY 1990, award rates have been significantly higher. For example, the award rate in FY 1989 was 31.9 percent and in FY 1988 the award rate was 33.3 percent.

DOWNWARD NEGOTIATIONS

Mr. Early. Dr. Fauci, to what extent will there be downward negotiations in competing and noncompeting grants, respectively, under the budget request?

Dr. Fauci. Under the current budget request, we will be downward negotiating competing and noncompeting grants 10 percent.

Mr. Early. How does this compare to FY 1990 and FY 1989?

Dr. Fauci. In FY 1990, competing and noncompeting grants will be downward negotiated 12 percent. In FY 1989, competing was negotiated at 10 percent and noncompeting at 12 percent.

Mr. Early. Doctor, this would be the third year in a row of downward negotiations of 10 percent of greater. What cumulative effect are these reductions having on research projects?

Dr. Fauci. In FY 1991, we will be downward negotiating competing and noncompeting research project grants by 10 percent. These downward negotiations enable us to generate funds for ongoing competing projects and for new awards. However, the NIAID will make every attempt to keep the downward negotiation level near 10 percent. Downward negotiation levels greater than ten percent would significantly erode the ability of our grantees to conduct research.

RESEARCH PROJECT GRANTS

Mr. Early. In addition to the "traditional" investigator initiated basic research projects, what other types of activities are supported through the research project grant mechanism at your Institute?

Dr. Fauci. In addition to the "traditional" investigator initiated basic research project, other types of activities that are supported through the research project grant mechanism are Research Program Projects to support basic research conducted by a consortium of scientists focusing on an important research area and the First Independent Research Support and Transition Awards to enable new investigators to receive research funding. Also supported through the research project grant mechanism are the Cooperative Agreements, for our AIDS clinical trials and drug discovery and vaccine development basic research programs, and Small Business Innovation Research Grants.

Mr. Early. What is the average cost of a competing and noncompeting research grant at your Institute -- for non-AIDS and AIDS?

Dr. Fauci. In FY 1991 our non-AIDS grants will cost on average $190,794 for competing, and $191,551 for non-competing. The AIDS grants will cost on average $182,890 for competing, and $509,442 for noncompeting. The average cost of the AIDS non-competing grant pool is much higher because it includes the AIDS clinical trials which are awarded under the cooperative agreement mechanism which has a higher average cost than other grant mechanisms.

DOWNWARD NEGOTIATIONS FOR RESEARCH CENTERS

Mr. Early. Will there also be downward negotiations in the research centers program? What is the percentage reduction for non-competing and competing centers?

Dr. Fauci. Currently, we estimate that we will downward negotiate our centers by 10 percent in FY 1991.

RESEARCH CENTERS

Mr. Early. Exclusive of the AIDS program, does the NIAID plan to fund any new research centers in FY 1991? In what program areas?

Dr. Fauci. We do not plan to fund any new research centers in FY 1991.

Mr. Early. Are additional centers needed? Do we need to expand programs at existing centers?

Dr. Fauci. Ample scientific opportunities exist to expand our centers program. However, the fiscal restraints within the centers mechanism have not allowed us to expand the centers as much as the opportunities would allow.

CLINICAL TRIALS

Mr. Early. Will the NIAID be starting any clinical trials in FY 1991? If so, please provide a list of AIDS and non-AIDS trials that will be initiated.

Dr. Fauci. The NIAID will be initiating a clinical trial studying Asthma in African American and Hispanic children residing in the inner city in FY 1991.

Mr. Early. Are there any high priority clinical trials which are ready but cannot be initiated because of lack of funds in the FY 1991 request? If so, please provide a list of these, along with a brief description and the associated costs, including first year cost.

Dr. Fauci. Yes, we have several high priority clinical trials which are ready to be initiated but can not begin due to a lack of funds in the FY 1991 request. The following is a list of these clinical trials:

1. Efficacy Trial of a Live, Recombinant Cholera Vaccine

   There is no safe, effective vaccine for cholera, a disease that causes over 500,000 life-threatening cases of diarrhea and over 100,000 deaths a year in Asia alone. The NIAID has a strong commitment to research on cholera and cholera vaccine development. One dynamic locus of cholera vaccine research is the University of Maryland School of Medicine, where a great deal of the NIAID grant and contract funding has been devoted towards developing new cholera vaccines. The most promising candidate vaccine (named CVD 103HgR) to emerge from this intense effort is an oral formulation consisting of live, attenuated cholera bacteria that were modified by using recombinant DNA technology.

   Studies in over 300 adult volunteers in Maryland and Thailand have clearly shown that CVD 103HgR is safe, immunogenic, and -- in volunteer challenge experiments -- over 90 percent protective. Studies are currently under way in cholera endemic areas to test the safety and immunogenicity in children as young as two years old. If, as anticipated, the vaccine continues to be promising, there will be tremendous international interest to move into large-scale efficacy trials as soon as possible.

   This situation will therefore provide the ideal juxtaposition of need and opportunity for the NIAID to guide this vaccine through its final stages of testing and to see its long-term investment pay off. This trial is estimated to cost $1,500,000 in the first year with an estimated over all cost of $6,000,000 for the four years the trial is projected to run.

2. Efficacy Trial of Conjugated Pneumococcal Polysaccharide Vaccine in Children and Infants

   Streptococcus pneumoniae remains a major cause of pneumonia, bacteremia, meningitis and otitis media in the United States. This is responsible for high mortality rates and serious morbidity. The current available pneumococcal vaccine as composed is immunogenic and has an efficacy of 70 percent, but the vaccine is less immunogenic in infants, young children, and high-risk individuals. Prevention of pneumococcal disease in infants will, therefore, require the development of a vaccine that is effective in this age group.

   The development of glyco-conjugates of the seven most common serotypes in infants and young children is on target and by 1991 we will have enough vaccine for a large-scale Phase III trial. Because of our commitment to this effort and the active role the institute has played in the first phase of assessing pneumococcal disease, we feel it is important that our efforts continue in this area. Funding for this trial is estimated to be $200,000 for the first year with a total cost over its projected three year period of $600,000.

3. Prophylactic Therapy for Neonatal Herpes

Therapeutic trials of antiviral therapy for neonatal disease have clearly demonstrated that the earlier treatment is initiated, the better the outcome. The best currently available therapy is a 10 day course with intravenous acyclovir. However, the clinical outcome of this state-of-the-art therapy is miserably unsatisfactory for almost half of infected babies. A major challenge to improving therapy for these infants is the finding that virus replication in the newborn can cause irreversible neurologic damage before the infant is obviously ill. Therefore, the overwhelming consensus of the infectious disease clinicians, pediatricians, and obstetricians who participated in a NIAID Neonatal Herpes Advisory Workshop in November 1988, was that the optimal therapeutic strategy would be to identify infected infants prior to the development of clinical disease and treat them prophylactically with oral acyclovir, before the virus has the opportunity to invade the brain.

The demonstration that neonatal herpes infections could be successfully treated prophylactically, following identification of newborns at risk, would revolutionize current medical practice. The primary benefit would be the reduction or elimination of the almost 50 percent risk of death or neurologic damage for the 1,500 newborn infants in the United States who develop neonatal herpesvirus infections each year. This trial is expected to run five years with an estimated first cost of $920,750, and a projected total cost of $4,986,000.

4. ddI/Forscarnet/Ganciclovir

Cytomegalovirus (CMV) retinitis has been shown to affect approximately 10-25 percent of patients in the late stages of AIDS and is the major cause of blindness in these patients. Both forscarnet and ganciclovir have been shown to delay the progression of the retinitis in patients with AIDS, but with either therapy, the drug must be indefinitely administered by an intravenous infusion treatment which is associated with significant morbidity and mortality.

The FDA has recently given ddI a Treatment IND to allow for wider distribution among HIV infected persons who are intolerant to AZT. Since both forscarnet and ganciclovir will likely be used with ddI in the future, a pilot study is proposed to evaluate the tolerance of these agents given concurrently with ddI. This is estimated to be a one year trial with a projected cost of $1,718,000.

5. Efficacy Trial of Live, Attenuated Rotavirus Vaccine Administered Orally to Infants

In infants and young children, diarrheal diseases are a substantial cause of morbidity in the USA and of both morbidity and mortality in the developing countries. Rotaviruses are consistently found to be the single most important etiologic agents of severe diarrhea in infants and young children in both developed and developing countries, being associated with about 30-45 percent of such illnesses.

Thus, the need for a rotavirus vaccine is clear and compelling with the goal being the vaccination of infants. Rotavirus vaccines have been developed and the need for continued field trials with various formulations is urgent. This trial is estimated to cost $1,000,000 during the first year with an estimated total cost of $2,000,000 for the projected two years the trial is projected to run.

6. ddI/Interferon

Recent efforts have begun to evaluate the use of combinations of anti-retroviral drugs in treating HIV infection. In a recently completed study, we found that the combination of AZT and alpha-interferon had potential benefit in treating HIV-infected patients, as evidenced by declines in p24 antigen levels as well as by decreases in the number of cultures positive for HIV. However, this combination was associated with a high incidence of adverse reactions that limited the maximum doses of each drug that could be administered.

More recently preliminary studies have found that ddI has anti-retroviral properties in vivo as well. Moreover, toxicities associated with ddI are minimal and different from those seen with AZT and alpha-interferon. Since it is likely that combination therapy will be necessary to effectively manage HIV infection, evaluating potentially effective combination regiments as quickly as possible is imperative. This study would evaluate the combination of ddI and alpha-interferon at various dosages looking for dosages of each drug that are well tolerated in combination but that appear to have beneficial antiretroviral effects. This trial is estimated to run two years with a projected first year cost of $1,718,000 with a total projected cost of $3.436,000.

7. Immunotherapy of Recurrent Genital Herpes

Herpes Simples Virus Type 2 (HVS-2) infections recur regularly in approximately five to ten million Americans. While acyclovir is effective in the management in some patients with recurrent genital herpes, other therapeutic strategies are needed.

We are completing the first phase I trial of a recombinant HVS-2 glycoprotein vaccine in patients with recurring genital herpes. Preliminary data suggests the vaccine to be extremely well tolerated and immunogenic. By 1991 we should have broadened our experience with this vaccine sufficiently to begin the first controlled trial in which we would test whether the enhanced immunity to HVS-2 elicited by the vaccine would be sufficient to diminish the frequency or severity of recurrent genital herpes. This trial is estimated to run one and one-half years. The first year cost is estimated to be $216,000 with a total estimated cost of $300,000.

RESEARCH TRAINING

Mr. Early. Funds for research training were increased in the FY 1990 bill. In what fields is the NIAID increasing the numbers of research trainees?

Dr. Fauci. There is an urgent and pressing need for an increased cadre of trained scientist in every discipline. The funds provided in fiscal year 1990 will be used to fund training for microbiologists, immunologists, molecular biologists and virologists in fields such as AIDS, sexually transmitted diseases, asthma, fungal and parasitic diseases, and hepatitis.

FTE's

Mr. Early. Are employment ceilings still restricting intramural program activities? If so, in what way and to what extent?

Dr. Fauci. I feel that the full time equivalent (FTE) level in the FY 1991 President's budget is sufficient to allow our intramural program to effectively carry out its mission.

Mr. Early. Provide, for the record, a table displaying for FY 1980 through FY 1991, the number of FTEs for your intramural research program and for research, management and support allocated to AIDS and non-AIDS activities.

Dr. Fauci. The following table reflects our FTE allocations for fiscal years 1980 through 1990:

National Institute of Health
National Institute of Allergy and Infectious Diseases
FTE History

AIDS

	FY1980	FY1981	FY1982	FY1983	FY1984	FY1985	FY1986	FY1987	FY1988	FY1989	FY1990	FY1991
Intramural	0	0	0	12	35	36	36	60	87	107	131	153
RMS	0	0	0	0	10	10	21	59	71	122	175	190
Subtotal, AIDS	0	0	0	12	45	46	57	119	158	229	306	343

Non-AIDS

	FY1980	FY1981	FY1982	FY1983	FY1984	FY1985	FY1986	FY1987	FY1988	FY1989	FY1990	FY1991
Intramural	0	502	497	515	523	520	481	465	470	466	525	558
RMS	0	176	169	178	177	171	164	148	178	175	202	215
Subtotal, Non-AIDS	0	678	666	693	700	691	645	613	648	641	727	773

TOTAL

	FY1980	FY1981	FY1982	FY1983	FY1984	FY1985	FY1986	FY1987	FY1988	FY1989	FY1990	FY1991
Intramural	0	502	497	527	558	556	517	525	557	573	656	711
RMS	0	176	169	178	187	181	185	207	249	297	377	405
TOTAL, NIAID	0	678	666	705	745	737	702	732	806	870	1,033	1,116

Note: FTEs were not counted until FY 1981

USE OF ADDITIONAL FUNDS

Mr. Early. If an increase over the FY 1991 request is provided for non-AIDS activities, how would you use these additional funds? What would your priorities be?

Dr. Fauci. There are numerous scientific opportunities to be explored with the use of additional funds. First, I would seek to fund more investigator initiated research projects in the area of basic research; second, I would increase our cadre of research trainees; and third, I would fund those clinical trials that are ready to begin but that we are currently unable to fund.

RESEARCH INITIATIVES

Mr. Early. Will any significant new research initiatives or opportunities be lost or delayed by lack of funds in the FY 1991 budget? Please provide, for the record, a list of these along with a brief description and the funding requirements associated with each.

Dr. Fauci. Multidisciplinary studies on the structure and function of the immune system in health and disease will not be initiated as a result of budgetary constraints. The acquisition of new and more in depth knowledge about immune responses and reactions is necessary if we are to develop improved procedures for prevention, diagnosis and treatment of immunological diseases and of diseases having a major immunological component. This initiative is intended to promote the formulation of multi-faceted programs of research involving groups of experienced biomedical researchers whose research efforts would be focused on the fundamental aspects of immunology relevant to major immunological diseases and disorders. The cost of this initiative is estimated to be $1,500,000.

It is now possible through immunologic and genetic tests to identify certain individuals who will develop Insulin Dependent Diabetes Mellitus (IDDM) before their immune systems have completely destroyed the insulin producing Beta Islet Cells in the Pancreas. As shown in animal models, Immune Suppression in such individuals may prevent the disease. The NIAID and the NIDDK would like to initiate a study to explore this further in a study tentatively entitled "The Multi-Center Clinical Trial of Immune Suppression in Pre-Diabetes". It is estimated that the NIAID contribution of the joint study would be $1,000,000.

In addition to our clinical trials being unable to fund inventory, there are several highly promising research initiatives that will be delayed due to a lack of funds in FY 1991. In the area of tuberculosis, a national plan calling for the elimination of tuberculosis in the U.S. by the year 2010 has been put forward. The development of a vaccine to prevent tuberculosis is an important priority if we are ever to achieve any control of this infection. At present, an attenuated bovine mycobacterium (BCG) is used as a vaccine in many parts of the world. The efficacy of this vaccine has been questioned and it is clear that control of this infection will require the development of new vaccines. To accomplish this task it is necessary to support basic research on the nature of the immune response to Mycobacterium tuberculosis, to determine the antigens present in M. tuberculosis that elicit protective immune responses, to better understand the pathogenesis of this disease, and to determine those factors in the host and the bacterium associated with reactivation of infection. An initial investment of $1,000,000 would enable us to begin this effort.

Sexually transmitted diseases represent an enormous social, medical and financial burden on the population of the United States. Basic and clinical research on all of the common STDs (gonorrhea, syphilis, herpes, papillomatosis and chlamydia) is badly needed if effective vaccines are to be developed to prevent these infections. New developments in the generation of mucosal immunity must be explored with candidate vaccines generated to prevent STDs. This is particularly important in view of the recent discovery that STDs that produce ulcerative disease (herpes virus, chancroid and syphilis) are known to facilitate the transmission of HIV. Basic and clinical research to develop vaccines to prevent sexually transmitted diseases would cost $2,500,000.

People who have been accidentally exposed to HIV, such as health care and emergency workers, have been administered antiretroviral therapy (AZT) in the hope that the drug would prevent infection. Specialized toxicology studies are needed so that the therapies used for people who have been accidentally exposed have the lowest potential toxicity. A resource is needed to determine the safest therapies for preventing HIV infection in people who have been accidentally exposed to the virus. The initial first year cost to begin some of these studies is estimated to be $3 million.

Mr. Early. To what extent will there be major reductions in the scope of ongoing or new initiatives because of the FY 1991 funding levels? For the record, please provide a list of these along with a brief description and the amounts associated with each initiative.

Dr. Fauci. Two important efforts that are ready for expansion will have to be delayed. These are the further development of improved vaccines to prevent pneumococcal infection and vaccines to prevent group B streptococcal (GBS) infections. Both of these vaccines take advantage of the biochemical technique of chemically conjugating bacterial polysaccharides to protein carrier molecules. It is known that these polysaccharides contain the important antigens of these bacterial pathogens and that this conjugation procedure greatly enhances the host's immune response to the polysaccharide. We estimate that these trials would cost $1,250,000 for the pneumococcal vaccine and approximately $1,000,000 for the group B streptococcal vaccine.

Recent scientific breakthroughs support the importance of the NCVDG programs, which bring together and coordinate the efforts of scientists from academia, governments, and industry to investigate novel approaches to AIDS vaccine development. Because of these promising new developments, much work is needed to determine how to translate these findings into a human vaccine. The NCVDGs ensure that basic research advances will proceed as rapidly as possible to animal evaluation, manufacturing/scale-up, and human trials. This program is the major NIAID effort in HIV vaccine development. Expansion of this effort would cost about $1,000,000.

Patients with AIDS are highly susceptible to a wide range of opportunistic infections. Given the diversity and number of pathogens, expansion of current efforts is needed to identify more effective and selective antiinfective agents. The NCDDG brings together scientists from academia, governments, and industry to facilitate the discovery and rapid development of new agents that are active against opportunistic pathogens. Expansion of this vital program would cost $4,500,000.

ACCELERATED VACCINE DEVELOPMENT

Mr. Early. Dr. Fauci, what progress in accelerated vaccine development program can you report since last year?

Dr. Fauci. Tremendous progress has been made in this field since last year. Progress was made not only in making new vaccines available to the public but also in the development of newer vaccines. A new, live typhoid vaccine which is administered orally was licensed for use in the U.S. late last year. In addition, the conjugate Haemophilus influenzae vaccine was made available for infants down to 15 months of age. Within the laboratory new and promising developments in vaccine research have emerged. A new oral vaccine to prevent cholera, CVD-103HgR, was entered in clinical trial in collaboration with the World Health Organization and the U.S. Agency for International Development. In addition, two new vaccines for Group B streptococcal (GBS) infections are expected to be available for clinical trial soon. Approaches to stimulate effective mucosal immunity were also actively pursued. One such approach uses the intriguing technique of combining important antigens with a commonly used polymer of glycolic and lactic acid. This polymer material is used widely in medicine as the basis for resorbable sutures in surgery. It appears that incorporating antigens into this material also produces an enhanced immune response and, in addition, a heightened immune response at the mucosal surfaces. This finding is extremely important because it may point the way to the development of a whole host of vaccines that can be used to prevent mucosal infections. This includes the STDs (including HIV), many respiratory infections and the gastrointestinal infections. Moreover, it also appears that immunity can be derived by the oral administration of these polymers, raising the possibility that these vaccines can be administered orally instead of by injection. Finally, enormous progress has been made in the development of new acellular pertussis vaccine. At least twelve different candidate acellular pertussis vaccines are under study at this time.

Mr. Early. How much have you allocated for this program in FY 1990 and FY 1991, exclusive of AIDS activities?

Dr. Fauci. In FY 1990 and FY 1991, excluding AIDS, we have allocated $25,926,000 and $27,400,000, respectively.

Mr. Early. Could additional vaccines be included in the program if you had additional resources?

Dr. Fauci. There is no doubt that vaccine research and development is an extremely active and exciting field. The introduction of techniques that employ monoclonal antibodies and recombinant DNA has made it possible to obtain antigens that were previously impossible to obtain in sufficient quantities to study. Most importantly, basic research in immunology, microbiology and infectious diseases has improved our understanding of the host's response to infection and of the identity of antigens that are important in protection. Vaccines to prevent STDs are badly needed not only because they are important infections in their own right, but also because they facilitate the spread of HIV infection. Vaccines to prevent herpes virus infections are presently under laboratory investigation and will need clinical evaluation soon. In addition, the application of the technology of producing polysaccharide-protein conjugate vaccines has dramatically increased the possibility that effective vaccines to prevent group B streptococcal (GBS) and pneumococcal infections in infants will soon be a reality. Finally, vaccines to prevent severe respiratory and gastrointestinal infections need to be developed. New approaches to the development of effective mucosal immunity have emerged from the investment in basic research in immunology and these advances must be applied to the development of vaccines to prevent STDs, and respiratory or gastrointestinal infections.

Mr. Early. How much did you originally request for the accelerated vaccine development program?

Dr Fauci. Our original 1991 request, exclusive of AIDS, for accelerated vaccine development was $41,100,000.

SEXUALLY TRANSMITTED DISEASES

Mr. Early. NIAID finally established a separate STD Branch in December of 1988. What have you been able to accomplish in the past 12 to 13 months? What are your program plans for FYs 1990 and 1991?

Dr. Fauci. Since its inception in December 1988, the Sexually Transmitted Disease Branch has developed three major initiatives and organized five consensus-building conferences to address, in a systematic way, critical issues in STD research. In February 1990, the STD Branch awarded a program project grant to broaden and integrate research on the epidemiology, pathogenesis and immunology in HPV infections.

In March 1990, the NIAID will issue an RFA for Sexually Transmitted Diseases Cooperative Research Centers (STD CRCs) to begin the expansion of the NIAID's STD research effort. The STD CRCs will offer a systematic, sustained approach to STD research through a network of exceptionally high quality, multi-disciplinary, collaborative research environments. This network will be a long-term investment that will provide the flexible infra-structure with which to respond to changing STD research challenges in the United States.

In recognition of the critical need for rapid, inexpensive, technologically-appropriate STD diagnostics in resource-poor settings such as clinics in American inner-cities and in the Third World, the NIAID and the AIDS Program of the Agency for International Development hosted a two-day workshop which initiated dialogue among representatives from funding agencies, the academic community, service delivery organizations, and industry. The meeting initiated the formation of an interagency group to spearhead research and development efforts. In addition, in March 1990, the Institute reviewed responses to an RFA for the development and use of rapid, accurate diagnostic tests for agents of clinical importance including STDs. Awards are anticipated in July.

In September 1990, the NIAID and Center for Disease Control (CDC) will jointly convene an expert panel to discuss research, prevention, and management issues in PID. After reviewing insights gained during the past decade in the pathogenesis, natural history, etiology, diagnosis, and therapy of PID and its sequelae, this working group will develop detailed PID research recommendations for the 1990s. The Institute anticipates responding to these recommendations both by issuing an RFA for re-competition of the three existing PID Research Units, and by drawing upon those Units and the STD CRCs to solicit applications for multi-center clinical trials examining interventions to reduce the frequency and severity of long-term sequelae of PID, such as infertility and ectopic (tubal) pregnancy.

To develop an agenda for intervention-oriented behavioral research on STDs, and to define the NIAID's role in addressing that agenda, we have assembled an inter-disciplinary group of international experts in behavioral sciences, sexually transmitted diseases, epidemiology, biostatistics, clinical trials, and health education. The group is examining the spectrum and prevalence of sexual, health-seeking, and drug-use behaviors which alter an individual's risk of acquiring STDs, and addressing the design and analysis of intervention trials to change those behaviors.

We are also planning on issuing important publications, a NIAID report with recommendations on behavioral research for prevention and control of STDs and a monograph for the STD and Behavioral Sciences research communities on inter-disciplinary research needs, opportunities, and approaches for the 1990s.

Mr. Early. What resources (staff and funds) have been allocated for the STD program in FY 1990? How much is included in your FY 1991 budget request? For the STD Branch?

Dr. Fauci. In FY 1990, the branch was supported by five FTEs who managed an extramural portfolio of grants, contracts and training of $36.5 million and an intramural program of $4.3 million. In FY 1990 the number of FTEs increases to 6 and the extramural effort rises to $38.2 million with an intramural program level of $4.6 million.

Mr. Early. Do you feel that these resources are adequate? If not, what do we need?

Dr. Fauci. The level of funding to date has allowed us to make significant advances in STD research. However, additional funds are needed to take advantage of the many scientific opportunities we have identified in our STD research needs plan. This plan builds on the infrastructure created by the STD Cooperative Research Centers and the Pelvic Inflammatory Disease Research Units to implement initiatives in crucial areas such as pelvic inflammatory disease, behavioral interventions and vaccine trials. In order to achieve these objectives, approximately $21.4 million would be necessary in FY 1991 to expand our current activities and to initiate research in the areas mentioned above.

Mr. Early. The justification indicates that the NIAID plans to establish STD cooperative research centers. How many centers will be established and when to you plan to make awards?

Dr. Fauci. We anticipate establishing two to four Sexually Transmitted Diseases Cooperative Research Centers (STD CRCs). The earliest award date will be July 1, 1991.

Mr. Early. Are new funds included in your FY 1991 request for this purpose? If so, how much?

Dr. Fauci. Our FY 1991 request provides $4,200,000 for STD Cooperative Research Centers.

Mr. Early. How much did you originally request for this initiative?

Dr. Fauci. Our original FY 1991 request for STD Cooperative Research Centers was $6,300,000.

Mr. Early. The budget justification indicates that the Institute will support the same number of research centers in FY 1990 and FY 1991, with no increase in funds. How do you plan to fund these new centers?

Dr. Fauci. The STD Cooperative Research Centers are being funded as Cooperative Research Agreements under the research project grant mechanism and not through the research center mechanism.

Mr. Early. Can you report any progress in research on chlamydial infection? Has there been any progress in the areas of improving diagnostic tests and therapies?

Dr. Fauci. In the past year there has been progress in chlamydial pathogenesis and vaccine development. Progress towards vaccine development has been aided by the realization that there are two components of the immune response to chlamydia, a protective one and a deleterious one that is an integral part of the development of chronic chlamydial disease. It is now apparent that the molecular basis of these two responses must be completely defined if a

chlamydial vaccine is to be effective. Work done in animal models suggests that immune protection is possible.

There is compelling evidence to suggest that there is an immunological component to the development of trachoma, a chronic chlamydial disease of the eye, and investigators have also begun to explore the role of the immune response in the development of pelvic inflammatory disease and related infections as well.

Detection of chlamydial infection is the key problem in control of chlamydial disease. The majority of patients are asymptomatic, and the existing diagnostic tests are expensive and technically difficult. Two new methodologies have shown promise in detecting chlamydial DNA in tissue, in situ DNA and the use of PCR. However, our goal is to develop an accurate test that can be utilized in resource-settings, such as our inner-cities, where such sophisticated methodologies would be hard to employ. Towards that goal, an interagency working group is being established to stimulate the development of STD diagnostics, appropriate for resource-poor settings, with a chlamydial diagnostic to be the first type of test addressed by the group.

Effective therapy for chlamydial infections is available using relatively inexpensive antibiotics and resistance is rarely a problem. In contrast to gonorrhea, which can be treated with a single dose of medication, however, chlamydial infections require seven days of antibiotic treatment. Patient compliance is often inadequate to cure infections, particularly because symptoms usually resolve quickly, if they were present at all, leading the patient to assume a cure had been effected.

Mr. Early. How much has been allocated for chlamydia research in FY 1990 and FY 1991?

Dr. Fauci. In FY 1990 we have estimated a budget of $4,679,000 for chlamydia research and we project an estimated $4,968,000 to be expended in FY 1991.

Mr. Early. HPV seems to be one of the obstinate of the STDs. Has there been any progress in our ability to detect and eradicate HPV?

Dr. Fauci. Research on HPV has been hindered by the lack of culture systems capable of supporting vegetative viral growth and the absence of a relevant animal model. However, recently an in vivo culture system has been established in the mouse. The virus is grown in human tissue transplanted on to the surface of the kidney in immunosuppressed mice.

Many essential questions about mechanisms of persistence, tissue tropism, replication and oncogenicity in HPV infection remain unanswered. Recently more sensitive methods for diagnosing HPV infection, such as PCR, have been developed. With these technical advances it will be possible to study the natural history of HPV infection and the virus' role in tumorigenesis.

Mr. Early. Have we learned any more about the possible relationship of HPV to cervical cancer?

Dr. Fauci. The advent of PCR, an extremely sensitive technique for detecting microbiological organisms, has raised new questions about the relationships between HPV and cervical cancer. Because initial studies using PCR documented HPV infections in many "healthy" individuals, new and expanded epidemiologic studies have been designed. Although most experts currently consider HPV infection to be a risk factor for cervical cancer, a "final verdict" and an understanding of the mechanisms involved must await the results of additional studies.

Mr. Early. What coordination is there between the NIAID and the NCI on HPV research?

Dr. Fauci. HPV research is usually dually assigned to the NIAID and NCI. Grant applications focusing principally on the biology or immunology of carcinogenesis are referred for primary assignment to NCI, while applications focusing on the virus, itself, or papilloma syndromes are referred for primary assignment to the NIAID. Since some overlap is unavoidable, therefore, the program staff in the two Institutes communicate at an individual level about proposed initiatives, scheduled reviews, and receipt of high-quality applications.

Mr. Early. Last year you indicated that, in FY 1990, the NIAID hoped to award two new research units focusing on HPV and cervical cancer. Will you be able to fund these two new research units in FY 1990? If not, why not, and does your FY 1991 request include funds for this purpose?

Dr. Fauci. In February 1990, the STD Branch awarded a program project grant to broaden and integrate research on the epidemiology, pathogenesis and host immune response in HPV infections. Only one award was made on the basis of the scientific merit of the applications which were received.

Mr. Early. What are your research plans in the area of pelvic inflammatory disease for FY 1990 and FY 1991, and how much has been allocated for PID research in each of these awards?

Dr. Fauci. In September 1990, the STD Branch of the NIAID and the Division of STD/HIV Prevention of the Centers for Disease Control (CDC) will jointly convene an expert panel to discuss research, prevention, and management issues in Pelvic Inflammatory Disease (PID). After reviewing insights gained during the past decade in the pathogenesis, natural history, etiology, diagnosis, and therapy of PID and its sequelae, this working group will develop detailed PID research recommendations for the 1990's. The Institute anticipates responding to these recommendations both by issuing an RFA for re-competition of the three existing PID Research Units, and by drawing upon those Units and the STD CRCs to solicit applications for multi-center clinical trials examining interventions to reduce the frequency and severity of long-term sequelae of PID, such as infertility and ectopic (tubal) pregnancy.

The estimated allocations for PID research for FY 1990 and FY 1991 are $2.0 million and $2.1 million, respectively.

Mr. Early. The STD Branch hoped to initiative prospective cohort studies to examine interventions to reduce the frequency and long-term complications of PID. What is the status of this project? Are funds included in your FY 1991 request for this project?

Dr. Fauci. Funds have not been allocated to support this initiative. It is likely to be an expensive project that will require a substantial infra-structure of the type offered by the STD CRCs and the PID Research Units.

However, a true commitment to improving the health of American women demands that such studies be initiated, in light of the severe, irreversible, and costly complications of PID. Funds were, therefore, included in the FY 1991 request, and the STD Branch plans to issue an RFA in FY 1991 for a multi-center clinical trial.

Mr. Early. I understand that four new types of antibiotic resistant gonorrhea have emerged in the last decade. What is the NIAID doing to address this problem? How prevalent are STDs in teenagers?

Dr. Fauci. Spread of antibiotic resistance, a major problem in the control of gonorrhea, is mediated by DNA exchange. Recently two mechanisms for gonococcal DNA exchange have been described. Given these sophisticated mechanisms for DNA exchange which encourage antibiotic resistance, current treatment methodologies hold little hope of controlling gonorrhea. Consequently the Institute has invested heavily in research towards vaccine development. A number of promising vaccine strategies are being studied. Several stable surface components, thought to play a role in the pathogenesis of gonorrhea, have been identified and will be the basis for further studies.

The STDs are very prevalent in teenagers. For example, 25 percent of all cases of gonorrhea occur in young people 14-18 years old. This is due partially to their social immaturity, partially to their sense of invulnerability, and the fact that barrier methods are rarely used.

Mr. Early. Sexually transmitted diseases are all transmitted by the same route. Is it possible to prevent and control STDs with behavioral approaches that focus on the way these diseases are spread? Has the Institute become involved in these approaches?

Dr. Fauci. Although each sexually transmitted disease presents unique diagnostic, therapeutic and prevention challenges, all STDs share a common mode of transmission. A multi-pronged research approach that targets biomedical and behavioral determinants of STD transmission and development of STD sequelae is, therefore, likely to be highly productive in yielding important insights into prevention and control.

The Institute currently supports four grants examining condom use and other behaviors affecting risk of transmission of STDs including HIV infection. The NIAID also has convened two meetings to identify future directions for behavioral research related to STDs. Research needs and opportunities were examined and recommendations were made on the NIAID's unique role in behavioral research on STDs. Guidelines for the STD Cooperative Research Centers encourage intervention-oriented behavioral research which examines behaviors and their impact on STD rates.

Mr. Early. Are sexually transmitted diseases a particularly common or severe problem in adolescents? If so, why and what is the Institute doing about it?

Dr. Fauci. Yes, there are numerous epidemiological studies which document a high prevalence of STD and STD sequelae in youth. For instance, 25 percent of all cases of gonorrhea occur in young people 14-18 years old. There are a number of biological and behavioral factors which contribute to these problems:

- In adolescent females there are unique anatomical features of the cervix which increase the likelihood of chlamydial or gonococcal infection. And hormonal changes of puberty facilitate the growth of trichomonads.

- Young people are immunologically naive, increasing the likelihood that exposure to an STD will result in infection.

- Behavioral factors are important in transmission. Adolescents' sense of invulnerability to health risks often results in failure to take precautions. Adolescents frequently use no birth control or rely solely on oral contraceptives. Barrier methods are rarely used. Furthermore, in many cases, sexual partners do not have the social maturity to discuss STD risk or its prevention.

- Behavioral factors also contribute to the high incidence of STD sequelae in this age group. Adolescents often deny symptoms and even if the possibility of infection is acknowledged, they are often too embarrassed and frightened to seek treatment. Failure to comply with treatment and the tendency to self-prescribe antibiotics obtained from friends are important factors.

For this vulnerable segment of the population prevention, diagnosis and treatment of STDs are critical. Support of basic research as a foundation for the development of vaccines, as well as diagnostic and therapeutic advances continues to have high priority. In addition, a workshop on STD diagnostics was held in February 1990. This meeting specifically addressed the development of the type of STD diagnostics needed for the resource-poor clinical settings in which most adolescents are seen.

The Institute's behavioral research efforts which link behavioral and microbiological approaches also target populations such as adolescents. The new STD Cooperative Research Centers (STD CRCs) will provide a setting for this research. And the CRCs' outreach programs and demonstration projects will provide exciting opportunities to impact on those adolescent behaviors which are risk factors for STD transmission and STD sequelae.

Mr. Early. We keep hearing about the disproportionate impact of STDs on the health of women and infants. Is this a valid assessment and, if so, what is the Institute doing about it?

Dr. Fauci. The consequences of STDs are both more common and more serious in women than in men. Three of the most significant problems are upper genital tract infection or pelvic inflammatory disease (PID), adverse outcomes of pregnancy, and cervical cancer.

The NIAID currently supports three PID Research Units which investigate the early stages of upper tract infection and their diagnosis and treatment. In FY 1991, we plan to solicit applications for a prospective, multi-center study of interventions to reduce the frequency and severity of the long-term sequelae of PID. Both the PID Research Units and the new STD CRCs will provide excellent sites for these studies.

In one quarter to two thirds of acutely infected pregnant women, STDs are preventable causes of adverse outcomes of pregnancy such as fetal wastage, low birth weight, and congenital infection. The NIAID and the NICHD have co-sponsored a multi-centered study of the impact of vaginitis in pregnancy. We hope to build on the results of this study with additional basic and epidemiologic investigations and with subsequent treatment trials.

Some strains of human papilloma virus (HPV), the same organism that causes genital warts, are associated with cervical carcinoma which causes approximately 5,000 deaths in American women yearly. In addition to currently supported research, the Institute has just awarded a program project grant to stimulate an expanded, multi-facetted attack on the issue of how HPV causes its full spectrum of disease. Additional HPV projects are being solicited within the context of the STD CRCs.

Mr. Early. Has there been any improvement in attracting individuals to training in STD research?

Dr. Fauci. In the past we have had problems in attracting individuals to training in STD research. This was probably due, in part, to the fact that the Institute overall had more applicants than available FTTPs and that the lack of a branch focal point may also have hindered attraction of applicants in this field of research. With the creation of the branch in 1988, the infusion of additional FTTPs in 1990, and the fact that training is one of the top priorities for the branch in the 1990s, that this situation will be turned around. The STD Branch is currently developing a multi-pronged training initiative, planned for implementation in FY 1992, that will increase its institutional fellowship awards program to a significant degree.

HEMOPHILIA

Mr. Early. What steps has the NIAID taken to increase the involvement and participation of the Hemophilia community and Hemophilia treatment centers in AIDS clinical trials?

Dr. Fauci. The bringing of these patients into the NIAID clinical trials system will give them opportunities to participate in clinical research and be exposed to the newest therapies for HIV infection. The imminent development of a prominent role for the

National Hemophilia Foundation in HIV treatment research should greatly enhance our ability to serve the hemophiliac population.

Mr. Early. I understand that the rate of progression to ARC and AIDS is increasing in the Hemophilia population. What new initiatives is your Institute planning to address regarding this situation?

Dr. Fauci. We are currently negotiating with the National Hemophilia Foundation to develop for them a prominent role in HIV treatment research. In this new capacity, they would effectively function as an ACTU with multiple sites and have full scientific participation in protocol development and other scientific issues.

AIDS VACCINE

Mr. Early. Dr. Fauci, we have read recently about the use of a new vaccine to prevent an AIDS-like disease in monkeys. Could you please tell us about this and what implication this has for the development of a vaccine for humans and describe the NIAID's efforts towards AIDS vaccine development?

Dr. Fauci. Recent research findings in animal model systems are showing promise that developing a vaccine for HIV infection may be possible. Results of four groups of vaccine research studies showed a range of protection in animals vaccinated with SIV vaccines and then challenged with virus. In some experiments, animals were completely protected from infection by the vaccine, whereas in other experiments, animals were infected after vaccination, but were protected from disease progression. In these experiments, scientists have successfully used vaccines made from whole SIV, inactivated virus, and a preparation made from part of the SIV outer, or envelope, protein.

Because the SIV and HIV are so closely related and produce very similar types of disease, these studies provide hope that scientists may ultimately create an effective HIV vaccine, a possibility that was considered to be much more remote last year. Several teams of NIAID-supported researchers are moving ahead with these studies.

Mr. Early. Dr. Fauci, could you give the status of your efforts to test new AIDS drugs and describe your efforts to find new drugs to feed into the pipeline?

Dr. Fauci. The need for more effective and less toxic agents to treat HIV infection is clear. Several new agents currently under investigation show preliminary evidence of being less toxic to bone marrow cells than AZT, an attribute that may prove to benefit patients who cannot tolerate the drug. These drugs may prove to be safe and effective alone or in varying combinations with each other or with AZT.

This year, four new antiretrovirals entered phase I clinical trials: dideoxyinosine (ddI), N-butyl DNJ, soluble CD4, and dideoxy-didehydrothymidine (D4T). These initial studies will help determine the maximum tolerated dose and provide preliminary information on the antiviral effects of the drug as well as its ability to improve the status of the immune system. Researchers have completed a phase I trial of ddI showing a favorable initial response. A trial of ddC was also completed this year. Because ddC shows promise in limiting the viral replication and has a different toxicity profile than AZT, studies are comparing alternating regimens of zidovudine and ddC. Study of soluble CD4 is another promising area of research. This molecule serves as the receptor for HIV on human cells - by blocking the receptor, we may be able to prevent the virus from gaining entry into the cell. Laboratory studies are encouraging, and in a clinical trial, the drug appears to be well tolerated and may be beneficial, although the efficacy has yet to be determined.

We are also studying the drug probenecid, a widely used drug with very low toxicity, which may enable the body to use AZT more efficiently. A recent studies sponsored by our AIDS Clinical Trials Group (ACTG) showed that probenecid was highly effective reducing the metabolic clearance of AZT, raising the possibility that probenecid may be effective in reducing the daily dose of zidovuine required to treat HIV-infected patients. This capability has the potential to improve convenience and compliance.

The NIAID AIDS Clinical Trials Group will continue to test promising new therapies as they become eligible for clinical research. The considerable number of new potential antiviral drugs is highly promising and should significantly expand the repertoire of available therapies for treating HIV infection. As treatment options increase, scientists will be able to develop optimal therapies for people in varying stages of HIV disease.

INFLUENZA RESEARCH

Mr. Early. Dr. Fauci, we are certainly aware that we have had a major flu epidemic this year. What progress on influenza research do you have to report?

Dr. Fauci. This influenza season was notable for it's high percentage of influenza related hospitalizations and deaths, especially in those over the age of 65. During this influenza season an average of 8 percent of all physician visits were due to influenza, and as high as 6.1 percent of all hospitalizations were the result of influenza virus infections. Prevention of influenza virus infection, through vaccination, continues to be the major emphasis of NIAID's research approach for the control of this disease. Research and development of the live, attenuated influenza vaccine (ca vaccine) remains a major commitment of the Influenza Program. Recent studies have suggested that the vaccine might be especially valuable for use in children, a primary source of influenza transmission. In this population, the live, attenuated vaccine appears to afford a longer duration of protection than seen in the inactivated vaccine, is more protective than the inactivated vaccine, and also prevents wild type influenza virus from replicating, and therefore spreading to others. Clinical studies have also shown the live, attenuated vaccine to be at least as good as the inactivated vaccine in the general population, although it may not be as good as the inactivated vaccine in the elderly population. The NIAID is currently negotiating a joint research endeavor with a vaccine manufacturer that should accelerate the licensure of the ca vaccine. Interest in improving the inactivated vaccine is also of concern to the NIAID.

The Influenza Program is currently evaluating the use of alternative high growth influenza strains for use in the manufacturing of inactivated vaccine. Such strains could provide larger quantities of vaccine, in a shorter amount of time. This would have the advantage of allowing decisions regarding the strain of influenza virus to be used in the subsequent year's vaccine to be made at a time when more data was available. Clinical studies to evaluate the use of adjuvants to boost the immune response to inactivated vaccine are also planned. The NIAID remains committed to investigate alternative approaches for the control of influenza virus infections, such as the development of antiviral drugs. There is currently one licensed drug available for the prophylaxis and therapy of influenza A virus infections, amantadine (Symmetrel).

The future of targeted approaches towards the development of antiviral drugs appears promising. The NIAID supported basic scientists have made great strides in understanding the complex interactions involved in rendering the influenza virus non-infectious. Research involved in identifying critical structural and chemical moieties necessary for influenza virus infection and replication is actively being pursued. The consequence of such research has been increased activity in the design of chemical analogues which would perturb the structure and thus inactivate the virus. Preliminary reports have suggested that at least one compound has been made which demonstrates the predicted properties. This compound, which is active against both influenza A and B is currently being tested in animal models.

TROPICAL DISEASES RESEARCH

Mr. Early. Last year, we discussed the growing concern about the situation relating to research needs in tropical infectious disease, particularly the dwindling pool of scientists in tropical medicine and the need for developing a cadre of investigators for this field. Have there been any improvements? What do we need to do?

Dr. Fauci. The NIAID has continued to provide research support for investigator-initiated projects in tropical diseases. These investigators provide a nucleus of mentors for training new entrants into the field. Further enhancement of training and strengthening of our capabilities in tropical medicine will occur within the Tropical Medicine Research Centers (TMRC). These new Centers, will be located in or near an area of endemic tropical disease and will consist of programs in clinical, epidemiological and basic or applied research in one or more tropical disease subject areas. These areas are parasitology, medical entomology, and bacteriology and virology of tropical diseases and are related to the biology and immunology of host-parasite relations, pathogenesis, diagnosis, immunotherapy and immunoprophylaxis, chemotherapy and chemoprophylaxis, vector biology and control. An important function of the TMRC will be to provide a research facility where U.S. investigators will have an opportunity to conduct research and gain experience in the field which is not available in the United States. Since the rate of progress has been in direct proportion to the support available, expansion of ongoing programs could provide many opportunities for progress to alleviate human suffering due to tropical diseases. While basic research will add to our capability to understand the mechanisms of disease, the application of such knowledge in the field will require a considerable increase in the pool of scientists with the necessary training for work in endemic disease areas.

Mr. Early. What is the status of the Tropical Medicine Research Center Program?

Dr. Fauci. The NIAID anticipates funding from one to four Tropical Medicine Research Centers. The program was advertised in early FY 1990 and nineteen applications have been received. Tropical disease areas represented by these applications include Africa, South America and the Far East. The applications are presently in the process of being peer reviewed. Awards to the successful applicants will be made early in FY 1991.

Mr. Early. How much is being allocated for tropical disease research in FY 1990 and FY 1991?

Dr. Fauci. We will be allocating $37,159,000 in FY 1990 and $39,205,000 in FY 1991, for tropical disease research.

Mr. Early. What was your original request?

Dr. Fauci. Our original request was $58,908,000.

HEMOPHILIA RELATED AIDS

Mr. Dwyer. I was pleased to learn of the NIAID's commitment to the National Hemophilia Foundation to work to include HIV-positive hemophiliacs in clinical trials. As you know, my office has been in contact with the NIAID in order to obtain AZT and ddI for hemophiliacs in my state, because these individuals were unable to take part in clinical trials. What percentage of hemophiliacs are currently sero-positive for HIV?

Dr. Fauci. According to the National Hemophilia Foundation (NHF), about 50 percent of hemophiliacs in the U.S. are currently seropositive for HIV.

Mr. Dwyer. To what extent are hemophiliacs participating in new clinical trials?

Dr. Fauci. In collaboration with the National Hemophilia Foundation, we had planned a major clinical trial to determine whether AZT can deter or slow the progression of HIV infection in hemophiliacs. However, this trial has been terminated because of the positive results of protocol 019, a trial of AZT in asymptomatic non-hemophiliacs.

We are currently negotiating with the NHF to develop for them a prominent role in HIV treatment research, in which they would effectively function as an ACTU with multiple sites and have full scientific participation in protocol development and other scientific issues.

Mr. Dwyer. To what extent has the establishment of the "parallel track" benefited hemophiliacs and other previously under-represented groups?

Dr. Fauci. Parallel track as a concept has yet to be implemented, however, the Public Health Service is now in the process of developing draft policies and procedures. At the current time, the closest model we have to the planned parallel track program is the expanded access program for ddI. This program offers the drug ddI under a treatment IND and open label protocol to patients who are intolerant or failing AZT therapy and who cannot get into the controlled clinical trials. Because the program is being run by the Bristol-Myers-Squib Corporation, we have no specific demographic information on the participants. However, there are no limits on eligibility specific to hemophiliacs for either the trials or the expanded access.

PEDIATRIC AIDS

Mr. Dwyer. In New Jersey, the AIDS epidemic wears the face of a woman or infant more often than any other state. Five metropolitan areas in New Jersey have the unfortunate distinction of being among the 25 metropolitan ~~ares~~ areas with the highest incidence of Pediatric AIDS. Indeed, the incidence of cases has far exceeded previous estimates. What efforts are being made to include IV-users and the sexual partners of IV-drug users in AIDS clinical trials?

Dr. Fauci. The NIAID is using several means to increase the participation of minorities, the HIV-infected populations most affected by intravenous drug use, in our clinical trials. A new RFA under development, entitled the Expansion of the AIDS Clinical Trial Group to Underrepresented Minorities, is expected to appear in the NIH guide early this year with the first awards anticipated in the Fall of 1990. Recognizing the importance of collecting data that includes minorities, we are working to increase minority participation in our studies through this RFA by several means, for example, by including provisions for bringing the necessary social services to potential minority participants. Although we are making progress in recruiting minorities into the system, we have strengthened our resolve to increase minority representation even further in our studies.

Clinical trials that include women are particularly important because the numbers of women developing AIDS are increasing dramatically. Many HIV-infected women are of a minority background and/or sexual partners of IV drug users. Together with the expansion of the pediatric clinical trials units, we are establishing perinatal centers serving women in at-risk populations. This feature will provide for increased attention given to pregnant HIV-infected women and their children in AIDS clinical trials.

A newly begun initiative that brings treatment research to community-based clinics and physicians is the Community Programs for Clinical Research on AIDS (CPCRA). The CPCRA broadens research opportunities to women, minorities, and intravenous drug users and the clinicians who care for them.

In addition, we are currently conducting high-level discussions with the National Institute of Drug Abuse (NIDA) and the Health Resources and Services Administration (HRSA) exploring ways those two agencies can work together to address the problems of intravenous drug use and HIV infection.

Mr. Dwyer. It is my understanding that current research efforts are focusing on ways in which to inhibit the perinatal transfer of HIV from the infected mother to the fetus. At what stage is this research? To what extent could substance abuse inhibit any effective therapy which could block perinatal transmission?

Dr. Fauci. Ongoing AIDS pediatric clinical trials are looking at the effects of AZT in perinatally exposed infants to determine if AZT can prevent the transmission of HIV from mother to child during pregnancy or birth. The results of those studies are not yet available.

Several major epidemiologic studies are researching questions of transmission of HIV infection from mother to child. In FY 1988, we funded the Cohort Studies of Perinatal Transmission of HIV and Related Retroviral Infection to look at the mechanisms and cofactors of perinatal HIV transmission. This multicenter, prospective study is also looking at the effect of pregnancy on the natural history of HIV infection and the natural history of HIV infection in the infants born to HIV-infected women.

Two other studies are also researching these critical issues. The Women and Infants Transmission Study (WITS) is a collaborative, multicenter study at four sites in New York, Chicago, Boston, and Puerto Rico which will recruit approximately 700 infected women. A pilot study phase is currently underway. A second study, Maternal Factors Influencing Perinatal Transmission of HIV, addresses the natural history of pregnancies in infected and uninfected women with HIV, both drug and nondrug users. This study will be conducted at the University of Medicine and Dentistry of New Jersey, Newark, NJ. A pilot study phase is currently underway.

Studies in basic science are also increasing knowledge of the mother-to-child transmission of HIV. Scientists have developed a mouse model of a retrovirus that produces an AIDS-like disease in small animals. Infected mothers can transmit disease to their offspring during birth and nursing. Drugs are being tested in this model for efficacy against these forms of retroviral transmission. Investigators have also developed a heterosexual transmission model for simian immunodeficiency virus (SIV) infection. This model, used to study potential drugs that may prevent transmission, has already given us insights into heterosexual retroviral transmission.

Regarding the effects of substance abuse on therapy, researchers are well aware than in an environment in which substance abuse plays a key role compliance with treatment of any kind is severely compromised. Thus, even if a perfect therapy existed, it would not have an equivalent impact to the same therapy taken in a non-drug using environment.

Mr. Dwyer. To what extent is the NIAID working with the NIDA to develop methodologies to track inner-city, HIV-positive, drug abusers?

Dr. Fauci. The NIAID is negotiating a formal agreement with the the NIDA to explore ways we can work together to address the problems of intravenous drug use and HIV infection. Both agencies believe strongly that the control of HIV infection in the intravenous drug using population is key to containing and conquering the epidemic in this country. The program will be implemented this fiscal year and will involve increased recruitment of intravenous drug users into the ACTG clinical trials.

LYME DISEASE

Mr. Dwyer. New Jersey is also an endemic state for Lyme Disease. Unfortunately, some physicians in my state believe that too little attention has been focused on improved testing as well as treating the chronic relapses which affect some Lyme Disease sufferers. What efforts are underway to control the deer tick and other arthropods which carry the infection responsible for Lyme Disease, Borrelia burgdorferi?

Dr. Fauci. At present there are no effective approaches to reducing the vector population in large areas. We are funding the research that is focused on increasing our understanding of the ticks which are the primary vectors of Lyme disease, Ixodes dammini, I. pacificus, and I. scapularis. It is expected that data generated by these research projects may provide clues that will lead to the development of effective strategies for controlling these vectors or interrupting the life cycle of B. burgdorferi in the vectors or reservoirs.

Mr. Dwyer. A recent breakthrough in Lyme Disease diagnostics will lead to a higher number of reported cases. Unfortunately, the large number of false negatives from the old test has lead some physicians to believe that "Lyme hysteria" was worse than the actual disease. What efforts will the NIAID make to make physicians aware of the new test and to encourage physicians to retest their patients.?

Dr. Fauci. Our Office of Communications, in cooperation with the NIAMS and the Lyme Borreliosis Foundation, is preparing educational posters and literature aimed at health professionals to aid them in dealing with victims of Lyme disease. At present these materials do not address the PCR test since it is not currently available as a routine application for the diagnosis of Lyme disease. When the test is fully developed and ready for general use, it will be incorporated into future educational campaigns in which we will participate.

Mr. Dwyer. What research efforts are underway to study those Lyme Disease patients who do not respond to short-term treatments with antibiotics?

Dr. Fauci. The NIAID is not currently supporting research in this specific area. However we are interested in funding studies that address this problem as are our colleagues at NIAMS. We are currently supporting research that may yield information that will form a basis for new approaches in treating these individuals. Research supported by the NIAID aimed at understanding how B. burgdorferi establishes infections and how it evades the immune system should also provide clues indicating how it may also evade the action of antibiotics that should have been effective. Such information should lead to a strategy for eradication of organisms that evade conventional antibiotic therapy.

Mr. Dwyer. What is in store for those individuals who seem to suffer from chronic relapsing infection from Lyme Disease?

Dr. Fauci. At present, patients suffering from chronic, late stage Lyme disease are treated aggressively with antibiotics. Several different antibiotics can be used in these treatments, often with positive effects. Unfortunately this is not always the case and the patient continues to be chronically ill. No effective alternative treatment protocols for application to these refractile cases have been identified. It is anticipated that research focused on pathogenic mechanisms and pathogenesis in animal models may provide clues that will lead to the development of new approaches to treating late stage chronic victims of Lyme disease.

VACCINES

Mr. Hoyer. What is the status of the gp160 AIDS vaccine and any immune therapy techniques and anti-viral drugs that the NIAID is involved with?

Dr. Fauci. The gp160 vaccine has been tested in 72 patients at two dose levels, 40 and 80 mcg., administered three times: the initial vaccination, and at one month and six months following. We then expanded the protocol and gave the volunteers another boost at 18 months. The results from our clinical trial have shown no safety problems, i.e., no toxicities, severe local reactions, or changes in laboratory parameters such as CD4+ cell counts. The vaccine did result in the production of neutralizing antibodies following the six-month booster. The trial is currently being expanded to include a higher dose.

Regarding the development of antiviral drugs and immune therapy, preliminary data on the safety and efficacy of ddI, thus far, looks very promising, and we hope that it will be beneficial. In a recently completed a phase I trial of ddI in patients with AIDS or symptomatic HIV disease, the drug was well-tolerated, producing almost no adverse clinical effects. In these preliminary studies, some patients showed improvement in their immune responses or decreases in viral activity. Because ddI and the other nucleoside analogs have a different toxicity profiles from AZT, these drugs may benefit patients who cannot tolerate AZT or may be used cyclically together with AZT or perhaps another drug.

Mr. Hoyer. Several PHS agencies are involved in the effort to eliminate TB, and I would like you to tell us about the NIAID priorities in this area for FY 1991?

Dr. Fauci. In recent years, new developments in the basic sciences have led to improvements in the prevention, diagnosis, and treatment of many infectious diseases. However, many promising techniques and procedures have not been applied or studied in relation to tuberculosis. These new techniques and procedures include deoxyribonucleic acid probes for rapid, specific detection of bacilli; serologic tests with monoclonal antibodies to detect antigens in body fluids; radiometric and cell culture procedures for rapid, accurate drug-susceptibility tests; development of new drugs and new drug delivery systems; new preventive therapy regimens based on a better knowledge of the characteristics of the infecting organisms and the host; and new vaccines based on a more thorough knowledge of host immunity and characterization of protein antigens.

The NIAID's priority areas of tuberculosis research for FY 1991 will be the development of an effective vaccine to prevent tuberculosis infections, which would have a monumental effect on public health; the improvement of diagnostic methods, which would enable public health authorities to respond quickly and more effectively to outbreak situations; the development of therapies that are inexpensive to administer, have low toxicity, and are effective over a shorter course of treatment; and a better clarification of the pathogenesis of *M. tuberculosis* to allow more precise analysis of virulence by which this pathogen survives and multiplies within the macrophage.

SEXUALLY TRANSMITTED DISEASES

Mr. Hoyer. The NIAID STD Branch was established in 1988. What are some of the initiatives in the STD Branch in 1990 and for FY 1991?

Dr. Fauci. The Sexually Transmitted Disease (STD) Branch has developed three major initiatives and organized five consensus-building conferences to address, in a systematic way, critical issues in STD research in the 1990s. In February 1990, the NIAID awarded a program project grant to broaden and integrate research on the epidemiology, pathogenesis and immunology in human papilloma virus infections.

In March 1990, the NIAID will issue an RFA for Sexually Transmitted Diseases Cooperative Research Centers (STD CRCs) to begin the expansion of the NIAID's STD research effort. The STD CRCs will offer a systematic, sustained approach to STD research through a network of exceptionally high quality, multi-disciplinary, collaborative research environments. This network will be a long-term investment that will provide the flexible infra-structure with which to respond to changing STD research challenges in the United States.

In recognition of the critical need for rapid, inexpensive, technologically-appropriate STD diagnostics in resource-poor settings such as clinics in American inner-cities and in the Third World, the NIAID and the AIDS Programme of the Agency for International Development hosted a two-day workshop which initiated dialogue among representatives from funding agencies, the academic community, service delivery organizations, and industry. The meeting initiated the formation of an interagency group to spearhead research and development efforts. In addition, in March 1990, the Institute reviewed responses to an RFA for the development and use of rapid, accurate diagnostic tests for agents of clinical importance including STDs. Awards are anticipated in July.

In September 1990 the NIAID and Center for Disease Control (CDC) will jointly convene an expert panel to discuss research, prevention, and management issues in PID. After reviewing insights gained during the past decade in the pathogenesis, natural history, etiology, diagnosis, and therapy of PID and its sequelae, this working group will develop detailed PID research recommendations for the 1990s. The Institute anticipates responding to these recommendations both by issuing an RFA for re-competition of the three existing PID Research Units, and by drawing upon those Units and the STD CRCs to solicit applications for multi-center clinical trials examining interventions to reduce the frequency and severity of long-term sequelae of PID, such as infertility and ectopic (tubal) pregnancy.

To develop an agenda for intervention-oriented behavioral research on STDs, and to define the NIAID's role in addressing that agenda, we have assembled an inter-disciplinary group of international experts in behavioral sciences, sexually transmitted diseases, epidemiology, biostatistics, clinical trials, and health education. The group is examining the spectrum and prevalence of sexual, health-seeking, and drug-use behaviors which alter an individual's risk of acquiring STDs, and addressing the design and analysis of intervention trials to change those behaviors.

We are also planning on issuing two important publications. One is a NIAID report with recommendations on behavioral research for prevention and control of STDs. The second is a monograph for the STD and Behavioral Sciences research communities on inter-disciplinary research needs, opportunities, and approaches for the 1990s.

Mr. Hoyer. Can you update the committee on any significant findings that were the result of the five consensus development conferences organized to address issues in STD research in FY 1989?

Dr. Fauci. Of the five conferences that the NIAID has organized since its inception in December 1988, two were held in FY 1989, two were held in early FY 1990 and a third is planned for September 1990. Significant or anticipated results of the conferences include:

- Herpes vaccine development: In July 1989, the NIAID convened a workshop on herpes simplex virus (HSV) vaccine development to review and evaluate current approaches in this field and to discuss future strategies and priorities. Several promising vaccine candidates are now available, and two Phase I clinical trials are in progress or have recently been completed. Additional trials are anticipated within the next 2-5 years. A summary of this workshop and its recommendations is in preparation.

- Behavioral research: To develop an agenda for intervention-oriented behavioral research on STDs, and to define the NIAID's role in addressing that agenda, the NIAID has assembled an inter-disciplinary group of international experts in behavioral sciences, sexually transmitted diseases, epidemiology, biostatistics, clinical trials, and health education. The group met in November 1989 and examined the spectrum and prevalence of sexual, health-seeking, and drug-use behaviors which alter an individual's risk of acquiring STDs, and is addressing the design and analysis of intervention trials to change those behaviors. Two important publications are planned: 1) a NIAID report with recommendations on behavioral research for prevention and control of STDs and 2) a monograph for the STD and Behavioral Sciences research communities on inter-disciplinary research needs, opportunities, and approaches.

- International STD research activities: In September 1989, the NIAID, in collaboration with the STD Programme of the World Health Organization (WHO), convened an expert panel to examine global STD research needs, opportunities, and constraints. The panel emphasized the urgent need for research in areas such as: 1) simple, rapid, inexpensive diagnostic tests (particularly for women); 2) vaccine development; and iii) female-controlled prevention technologies such as female condoms or bactericidal/virucidal intravaginal preparations. The report and recommendations of the panel were published by WHO in January 1990. The Institute plans to continue to facilitate international STD research activities by helping to establish the WHO STD Programme's Research Advisory Group, which was recommended by the panel.

- Development of STD diagnostics: In February 1990, the NIAID in concert with the AIDS Programme of the Agency for International Development, hosted a two-day workshop on the development of STD diagnostics for resource-poor settings such as clinics in American inner-cities and in the Third World. The group determined that the three most urgent needs for STD control in such settings are, in order of priority: 1) rapid, inexpensive, and easy-to-use tests for chlamydial infection and for gonorrhea in women; 2) analogous tests for syphilis and chancroid; and 3) more systematic and skilled use of Papanicolaou (Pap) smears. The consensus of the workshop was also that the limiting constraint on design of such tests is no longer biotechnology, but rather test format, marketing and distribution costs. The meeting initiated the formation of an interagency group to spearhead research and development efforts.

- Pelvic inflammatory disease (PID): In September 1990, the NIAID and the Division of STD/HIV Prevention of the Centers for Disease Control (CDC) will jointly convene an expert panel to discuss research, prevention, and management issues in PID. After reviewing insights gained during the past decade in the pathogenesis, natural history, etiology, diagnosis, and therapy of PID and its sequelae, this working group will develop detailed PID research recommendations for the 1990s as well as formulate national PID prevention and management guidelines.

AIDS EDUCATION EFFECTIVENESS

Mr. Hoyer. Does the NIAID's natural history or other studies reveal any useful information on the effectiveness of education efforts intended to promote changes in "at risk" behavior?

Dr. Fauci. The Multicenter AIDS Cohort Study and San Francisco Men's Health Study are two examples of the positive effect of education on limiting the spread of HIV infection. Besides gathering critical epidemiologic data on the natural history of HIV infection, these studies have an active component involved in education and counseling at all their centers. These functions extend into the communities in which these studies are located, to both the gay community and the community at-large. For example, these studies are considered to be the most important educational resources in their communities and are involved in a wide range of educational efforts, such as advising local government at the highest level on outreach issues. Data coming from these studies on the numbers of people who annually seroconvert reveal that since 1984 the number of people becoming infected with HIV has declined dramatically. This fact would indicate the benefits of a strong community outreach resource.

AIDS

Mr. Hoyer. The definition of AIDS research at the NIAID was broadened in FY 1990 to include grants that had earlier been classified as non-AIDS. Why?

Dr. Fauci. Finding drugs and vaccines for HIV infection depends heavily on broad-based basic research in a variety of scientific fields, such as immunology, molecular biology, virology, molecular genetics, and cell biology. In addition, the development of resources, such as animal models, has a great ability to apply to a wide range of research project. Thus, we made the decision that research that was highly relevant to HIV infection should be funded as AIDS-related research. This action made it possible for us to fund very important research grants that would have otherwise gone unfunded.

Mr. Hoyer. What is your opinion of the views expressed in the press that AIDS is becoming a "manageable chronic" condition?

Dr. Fauci. I am in complete accord with this view. As new drugs are brought from our clinical trials to the clinics and to physicians who care for AIDS patients, the potential grows for these patients to lead longer lives with a higher quality of life. We have already seen evidence that death rates from AIDS are diminishing due to the effect of treatment. These trends are very promising and raise hope that HIV infection will be a manageable condition for people infected with the virus.

Mr. Hoyer. Can you explain the differences in attention and support for efforts to fight the HIV infection compared to the opportunistic infections that destroy the lives of people with AIDS, and what are your views on these differences, particularly as it impacts anti-viral drug development?

Dr. Fauci. One of the major goals of the NIAID is to stimulate research to discover and develop therapeutic agents for treating opportunistic infections (OIs). These diseases are the major causes of illness and death in AIDS patients and contribute significantly to the medical costs of treating HIV-infected people. HIV-infected patients are susceptible to a wide range of protozoal, fungal, viral, and bacterial infections, whose management is difficult and complicated because: (a) patients are often affected simultaneously by several opportunistic infections, (b) the pathogens may develop resistance to conventional therapies, and (c) AIDS patients are more susceptible to drug-related toxic reactions. Further, most currently available therapies against the opportunistic infections in AIDS patients either have limited efficacy or potentially serious side effects.

Because of the need to intensify research efforts to understand and control these organisms, we have begun a comprehensive, integrated effort to increase research in the OIs, the NIAID coordinated OI program; awards are expected in June 1990. The program encompasses: (1) the National Cooperative Drug Discovery Group (NCDDG)-OI effort, (2) basic investigator-initiated research grants, (3) contracts for screening agents to treat opportunistic infections, (4) animal model contracts to analyze the efficacy and toxicity of single and combination therapies, and (5) resources necessary for the preclinical development of therapies for OIs.

This vital new initiative will augment ongoing work, which has already produced results. For example, our screening program results in the screening of hundreds of compounds a year for activity against many of the key opportunistic organisms affecting AIDS patients. These studies have led to the identification of promising drugs, such as the combination of clindamycin and primaquine as treatment and prophylaxis for PCP, now under study in ACTG-sponsored clinical trials.

ACCESS AND EFFECTIVENESS

Mr. Hoyer. The NIAID announced 18 community-based programs for clinical training this past October. What are the NIAID's plans or expectations for the CPCRAs in FY 1991?

Dr. Fauci. This program was just funded, and three protocols are soon to be activated for study by the CPCRA. The community clinicians and Principal Investigators of the CPCRA have decided the most appropriate first work of the group should be the development and implementation of the following studies:

- A study comparing two widely used agents for the prevention of toxoplasma gongii encephalitis in persons with HIV infection. Toxoplasma encephalitis is an opportunistic infection which frequently occurs in persons with late stage HIV infection which may be prevented or delayed with appropriate prophylaxis.
- A study of the comparative efficacy of ddI versus ddC in patients with HIV who are intolerant to or have failed AZT therapy.
- An observational database project which will assist community clinicians in regular assessment of clinical and therapeutic patterns among all their patients as well as the potential to answer important questions about changing patterns of HIV disease and care of persons with HIV infection.

The community clinicians of the CPCRA have self-selected into relevant interest groups from which ideas for multi-site studies will initiate in collaboration with the medical, statistical and methodologic input from the NIAID staff. These interest groups are as follows: antiretroviral therapies, opportunistic infection prevention and treatment, observational database project, and patient care and special populations/compliance.

Mr. Hoyer. What steps has the NIAID taken to improve the access of children to the AIDS clinical trial groups?

Dr. Fauci. The NIAID is sponsoring a new initiative that will further expand our efforts to reach HIV-infected children; awards are expected to be made in the Fall of 1990. In addition, we have also strongly encouraged the AIDS Clinical Trials Units that accrue primarily adults to begin pediatric studies as well. As a result, several sites have begun these vital studies. Another important component to the expansion of pediatric trials units is the establishment of perinatal centers serving women in at-risk populations. This feature will provide for increased attention given to pregnant HIV-infected women and their children in AIDS clinical trials.

Mr. Hoyer. To what extent has the NIAID coordinated with the HRSA HIV-related programs to improve access to trials and better treatment options for the various AIDS-impacted populations?

Dr. Fauci. The NIAID has met several times with representatives from the Health Resources and Services Administration (HRSA) to explore the possibility of bringing our complementary resources together to address the needs of intravenous drug users. The approaches under consideration may be effective in reaching this population because they combine HIV treatment research, which is difficult to do in intravenous drug users, with other much needed activities, such as primary care and drug abuse treatment. Specifically, the NIAID may link our AIDS Clinical Trials Units with some of the new Bureau of Health Care Delivery and Assistance (BHCDA) grants, which are targeted to provide substance abuse treatment and care to intravenous drug users.

Mr. Hoyer. Can you elaborate on the NIAID's efforts to assure that pediatric clinical trials are appropriately expanded?

Dr. Fauci. Over 370 HIV-infected children and adolescents currently participate in clinical trials for AIDS drugs. The AIDS epidemic has hit minority children particularly hard with eighty-nine percent of the pediatric AIDS patients being African American or Hispanic. To address their special needs, we have increased the number of pediatric AIDS clinical trials units receiving funding to 15, enabling researchers to begin phase II and III trials in children.

The NIAID will sponsor a new initiative, soon to be published, that will further expand our efforts to reach HIV-infected children with awards expected to be made in the Fall of 1990. We have also strongly encouraged the units that accrue primarily adults to begin pediatric studies as well. As a result of this initiative, several AIDS Clinical Trials Units (ACTUs) have begun these vital studies. Another important component to the expansion of pediatric trials units is the establishment of perinatal centers serving women in at-risk populations. These centers will provide for increased attention given to pregnant HIV-infected women and their children in AIDS clinical trials.

Mr. Hoyer. How near are we to closing the gap caused by our relatively late focus on the particular research, diagnosis, and treatment problems associated with pediatric AIDS?

Dr. Fauci. There are currently 42 drugs and drug combinations in HIV clinical trials. Several distinct drugs as well as a number of drug combinations are being tested in children with HIV infection, including AZT, intravenous immune globulin (IVIG), dideoxyinosine (ddI), and aerosolized pentamidine. Protocols are in development for hyperimmune anti-HIV IVIG, dideoxycytidine (ddC), and recombinant CD4. It is essential that we be much more selective in our approach to choosing drugs for study in children because of the much smaller number of children infected and therefore potential candidates for study, and the low likelihood of success.

WOMEN IN RESEARCH

Mr. Hoyer. What is the NIH and the NIAID policy with respect to the inclusion of women in AIDS and other trials?

Dr. Fauci. The NIAID's policy is to offer enrollment in its clinical trials to all eligible parties. People are excluded from the studies only when there are specific scientific or safety criteria necessitating an exclusion. There are never arbitrary exclusions on the basis of sex.

Mr. Hoyer. Could you provide the committee a list of AIDS trials currently underway with information on the number of women participants?

Dr. Fauci. First, let me address the issue of women in our AIDS clinical trials. In FY 1989, 11 percent or 735 of our total AIDS clinical trials population were comprised of women. They participate in the studies to a higher degree than their numbers affected by the disease, which is nine percent of AIDS cases in the United States. These numbers indicate that women are well represented in the NIAID clinical trials system. Further, several studies specifically address the needs of HIV-infected women.

Currently, AIDS clinical trials are being conducted at the following institutions:

Albert Einstein College of Medicine (2)*
Atlanta AIDS Research Consortium, Inc.
Baylor College of Medicine (2)*
Bellevue Hospital/New York University Medical Center (2) *
Bronx-Lebanon Hospital Center
Boston City Hospital
Children's Hospital Corporation
Children's Memorial Medical Center
Cornell University Medical College
Columbia University
Denver City-County Health Department
Duke University Medical Center (2)*
George Washington University Medical Center
Good Samaritan Hospital and Medical Center
Indiana University School of Medicine
Henry Ford Hospital
Hill Health Corporation
The Johns Hopkins Hospital
The Johns Hopkins University (2)*
Los Angeles County-University of Southern California Medical
Center Massachusetts General Hospital/Harvard Medical School
Memorial Hospital/Memorial Sloan-Kettering Cancer Center
The Milton S. Hershey Medical Center
Marshall University

Mount Sinai School of Medicine (2)*
National Hemophilia Foundation
NIAID Intramural Research Program (3)*
New Jersey Medical School
North Jersey AIDS Alliance
Northwestern University Medical School
The Ohio State University Medical Center
The Presbyterian Hospital/Columbia-Presbyterian Medical Center
Robert Wood Johnson Medical School
St. Luke's Roosevelt Hospital
San Francisco General Hospital,University of California
Stanford University School of Medicine
State University of New York Health Sciences Center
Tulane University (2)*
University of Alabama at Birmingham
University of California, Los Angeles Center for Health Sciences
University of California School of Medicine
University of California Medical Center (2)*
University of California, San Francisco (2)*
University of Cincinnati College of Medicine
University Hospitals of Cleveland
University of Maryland at Baltimore
University of Massachusetts Medical School
University of Miami School of Medicine (2)*
University of Minnesota Health Sciences Center
University of North Carolina School of Medicine
University of Pittsburgh School of Medicine
University of Rochester
University of Rochester Medical Center
University of Washington School of Medicine
Vanderbilt University
Virginia Commonwealth University
Washington University School of Medicine
Wayne State University

* Numbers in parentheses indicates the number of trials being conducted in that institution.

Mr. Hoyer. What research is currently under way to study gender differences in the development, course, and treatment of AIDS?

Dr. Fauci. Differences in disease outcome based on sex, race, or other factors have not been documented. However, several epidemiologic studies are gathering more detailed information on possible subtle differences, as yet unknown, that may exist in the course of HIV infection in various populations.

CHRONIC FATIGUE SYNDROME

Mr. Porter. What is the status of your efforts in the area of Chronic Fatigue Syndrome? What progress has been made since we discussed this last year?

Dr. Fauci. We currently have three grant-supported studies of CFS in progress. A 3-year case-control study by a NIAID supported investigator in Denver will be completed at the end of this year. Another NIAID supported study is devoted to estimating prevalence of CFS and is using a county-based HMO population. This study has a built-in case-control design which will provide data on risk factors, pre-illness medical history, diagnostic markers and 2-year disease progression. A third study recently awarded will compare multiple sclerosis patients and CFS patients who show the most objective signs of neurologic impairment. The latter is a very comprehensive study which will include neurologic, immunologic and virologic components. We expect these interrelated studies to help us estimate the true magnitude of the problem and to provide important new information about the syndrome and its clinical expression, precipitating factors, diagnosis and patient characteristics. New methodologies for monitoring disease activity are also being assessed in the course of these and our own intramural studies.

With regard to progress in our understanding of the syndrome, the findings reported by the NIAID investigators studying patients in the NIAID cohort may be the most important. Their results suggest that CFS patients have neuroendocrine pattern differences when compared to healthy controls and patients with typical clinical depression. The neuroendocrine pathway is critical in handling stress and is known to be influenced by a variety of disease processes. This provides a clue regarding the underlying constitutional factors which make CFS patients appear to be more susceptible to allergies, prolonged convalescence from infections, and psychiatric disorder.

Mr. Porter. How many extramural research grants related to CFS are you currently funding?

Dr. Fauci. In FY 1989, the NIAID funded three extramural grants and one intramural project related to Chronic Fatigue Syndrome. In FY 1990, the Institute plans to maintain the same portfolio in CFS.

Mr. Porter. Do you see merit in establishing a research center for CFS?

Dr. Fauci. We in fact have a centers-like effort right now. We have awarded two grants to a principal investigator at Harvard University and he is collaborating with more than 14 investigators including neurologists, internists, immunologists, virologists and psychologists.

Mr. Porter. Do you see any merit in imposing a program whereby we collect clinical data on CFS patients in a number of locations through the use of standardized methods?

Dr. Fauci. The use of a multicenter approach can be very useful for the study of certain diseases. Unfortunately, CFS does not lend itself to that kind of approach nor do I think that it is necessary at this time in order to advance the field. First, we do not currently have a single immunologic, virologic, clinical marker nor constellation of markers on which to base a definitive diagnosis or an assessment of clinical exacerbation or remission. Even the current CFS case criteria are slated for revision. Second, it is extremely difficult to obtain comparable standardized clinical data at different centers under the best of circumstances, making such an approach presently unfeasible for chronic fatigue syndrome because of the subjective nature of the assessment of clinical signs of interest and the variability of many of the laboratory measures being studied. Ongoing research here at the NIAID, at the CDC and at the NIAID grantee institutions is attempting to address this problem by defining appropriate markers and methodologies under carefully controlled conditions which might be applied at a later time. Third, there are sufficient CFS cases at the individual research centers throughout the country to make single-center studies feasible.

Mr. Porter. How about the collection of psychological state, and cognitive function data, again through a standardized method?

Dr. Fauci. Again, although the idea of applying standardized methods is sound, it is premature to consider a multicenter approach for the reasons outlined in the previous response. I do consider the use of such approaches to be an essential requirement for obtaining meaningful data. You may recall that the NIAID sponsored a conference to discuss problems in study design for CFS. A monograph based on that conference is nearing completion and will be available in the near future.

Mr. Porter. Have you considered a coordinated effort to collect data on CFS patients at times of apparent clinical exacerbation or remission of their symptoms?

Dr. Fauci. A NIAID investigator has just such a study underway. It would be very helpful to have a clinical or laboratory marker that would correlate with severity of symptoms. Not only would such a marker facilitate clinical studies, but it would also provide insight concerning pathogenesis of the syndrome.

Mr. Porter. What is the status of your efforts to coordinate CFS research with the CDC and the NIMH?

Dr. Fauci. Reports are received by the NIAID from other Institutes at the NIH, the CDC and the ADAMHA, of which the NIMH is a component, regarding their chronic fatigue syndrome intramural and extramural research programs and their efforts to disseminate information to the medical community and the public sector. Coordinated activities are considered essential because of the nature of the syndrome and the need for expertise from diverse agencies within the Public Health Service.

VACCINES

Mr. Porter. As the lead agency in vaccine development, can you tell me if there are any other candidate vaccines which would be ready for testing at this time if additional funds were available?

Dr. Fauci. Several vaccine candidates have progressed through the laboratory and are now ready for additional clinical evaluation. These include vaccines to prevent Group B streptococcus, hepatitis A virus, cholera, rotavirus, pneumococcus and several important respiratory viral infections such as respiratory syncytial infection and parainfluenza. Research on all of these vaccines could be significantly advanced with adequate resources and be ready for clinical trials to assess efficacy in the near future.

TROPICAL DISEASES

Mr. Porter. I've heard from a number of people that the NIAID should do more research on tropical diseases, and diseases in developing countries. Do you agree? What are you currently doing in this area?

Dr. Fauci. The NIAID has a long history of supporting research on tropical diseases, especially those diseases that are major health problems in developing countries. Currently, the NIAID plays a lead role in the support of tropical disease research at the NIH and is the primary source of funding in parasitic diseases, tropical microbiology and vector biology for investigators throughout the United States. A broad spectrum of research projects on host, parasite and vector relationships are funded with the ultimate goal of applying the basic information obtained to the control and treatment of tropical diseases in man. Tropical Disease Research Units conduct state-of-the-art research in domestic laboratories and collaborate with institutions in developing countries. The International Collaboration in Infectious Diseases Research Program supports domestic institutions who have a major commitment to conduct research programs on tropical diseases in developing countries. A new program, the Tropical Medicine Research Centers, will provide direct support to research facilities in areas of endemic tropical disease and will facilitate the enhancement of our nation's capabilities to address tropical disease problems.

RESEARCH PROGRAMS

Mr. Porter. I understand you've hired a number of people with nursing backgrounds and placed them in important positions within the Institute's research programs. Could you describe this effort and discuss future plans?

Dr. Fauci. We have a long history in the NIAID of actively involving nurses on our staff in our intramural research protocols. We have recently hired a number of nurses in our extramural Division of AIDS who are serving as program officers and are overseeing some of our clinical studies as well as some of the activities of the program related to regulatory affairs. In addition, we have developed a collaborative program with the National Center for Nursing Research in which we will be adding research on symptom management to some of our existing intramural clinical protocols. We are thus providing part of the facilities and patient resources for the NCNR's intramural research program. We certainly plan to continue the recruitment of nurses along with other health professionals in our extramural programs and to continue and expand our collaboration with the NCNR.

LYME DISEASE

Mr. Porter. In your opening statement you discussed potential applications for the polymerase chain reaction (PCR) technique. Among these you mentioned improved diagnostic techniques for Lyme Disease and chlamydial infections. How good is our current ability to diagnose Lyme Disease?

Dr. Fauci. An accurate diagnosis of Lyme disease is dependent on the attending physicians's abilities and familiarity with the range of clinical signs and symptoms of Lyme disease. Therefore, our current ability to properly diagnose Lyme disease no doubt varies with geographical location and a physician's experience. Physicians working in hyperendemic Lyme disease areas of the country are more experienced in detecting the many different and subtle clinical presentations of the infection. Serologic confirmation of Lyme disease is still problematic and the PCR will certainly improve laboratory confirmation of Lyme disease. The PCR has the potential to identify cases of Lyme's disease in patients who were diagnosed as something else or were not detected by other less sensitive testing procedures. The NIAID intramural scientists are completing work on preparing this assay system for commercial release and plan to have an early version of the PCR Lyme disease assay available within one year.

Mr. Porter. How will this improve using the PCR application?

Dr. Fauci. PCR is much more sensitive and specific than currently used serological tests. However, we need more experience in the application of this test to Lyme disease. In order for this test to work effectively, we have to know what sort of specimens will work best. The major requirement is that at least one borrelia must be present. If it is not in the sample, the PCR test will be negative. Thus, we must determine the best tissue site for efficient recovery of borreliae from infected patients. Greater understanding of pathogenesis will aid in achieving this goal.

Mr. Porter. How soon will the PCR diagnostic technique be generally available to the physician population?

Dr. Fauci. Researchers at the NIAID Rocky Mountain Laboratories have reported the development of a PCR test for the Lyme disease spirochete. Similar developments are in progress at several other U.S. laboratories. These are very exciting developments. However, it should be realized that at present this technology is not ready for general application in diagnostic laboratories and will not be generally available in the immediate future. The establishment of PCR in clinical laboratories requires rigorous procedures to ensure that clinical samples are not contaminated thus creating a problem with false positive test results. The PCR will require the purchase

127ecc

of new equipment and extensive training of personnel and this test, even when ready for general use, will probably remain as a backup for faster, cheaper and less complicated serological tests.

SEXUALLY TRANSMITTED DISEASES

Mr. Porter. What problems do we currently have in diagnosing chlamydial infections?

Dr. Fauci. Diagnosing chlamydial infection is a major obstacle in the control of this STD. The majority of infected women and a large number of infected men are asymptomatic. They do not know they are infected, and they do not seek treatment. A successful chlamydia control program, therefore, requires screening, treatment and partner notification in high risk populations. In this country these populations are most frequently found in resource-poor settings. In these settings such a screening program is dependent on the availability of rapid, inexpensive, easy-to-use diagnostic tests. These tests do not currently exist. As a result of a NIAID/AID cosponsored workshop held in February 1990, an interagency working group is being established to stimulate and coordinate the development of STD diagnostics appropriate for resource-poor settings. A chlamydial diagnostic will be the first type of test addressed by the group.

Mr. Porter. How widespread are these infections?

Dr. Fauci. Chlamydial infection is the most prevalent bacterial sexually transmitted disease (STD) in the United States. It is estimated that four million cases occur annually. Besides local infections of the genitourinary track, chlamydia also causes pelvic inflammatory disease which, through tubal scarring, may lead to infertility, ectopic (tubal) pregnancy, and chronic pelvic pain syndrome. In addition to genital disease, this organism is also responsible for eye disease in adults and children and pneumonia in infants born to infected women.

Mr. Porter. How soon will PCR diagnostic tools be generally available for chlamydial infections?

Dr. Fauci. Polymerase chain reaction, PCR, is a newly developed technique with extraordinary potential for sensitive and specific identification of infectious organisms. In research settings, PCR techniques are already capable of detecting as few as 1-3 chlamydiae in a biopsy specimen.

In its current form, this technique is not feasible for use in clinical settings because it is requires sophisticated technical skills, rigorously clean working conditions to prevent contamination of samples, and use of radioactive probes. However given the value of a method with this degree of sensitivity and specificity, it is likely that all of these obstacles will be dealt with in the near future. Adaptation of PCR for use in regional reference laboratories is imminent. Further adaptation to the resource-poor settings in which STDs are most prevalent will likely occur within the next decade.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

FY 1991 Budget	Page No.
Appropriation language and explanation of language change	126
Amounts available for obligation	127
Budget mechanism table	128
Crosswalk tables	130
Summary of changes	133
Budget authority by activity	135
Budget authority by object	136
Significant items in House and Senate Appropriations Committee reports	138
Authorizing legislation	150
Appropriations history	151
Justification:	
A. General statement	153
B. Program accomplishments	156
C. AIDS research program	168
D. Allergy, immunology and transplantation	179
E. Microbiology and infectious diseases	184
F. Intramural research	190
G. Research management and support	196
H. Detail of permanent positions	198
I. Advisory and assistance services	200

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

For carrying out section 301 and title IV of the Public Health Service Act with respect to allergy and infectious diseases, [$846,318,000] $886,875,000.

(Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 1990.)

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation................	$754,084,000	$846,318,000	$886,875,000
Enacted administrative reduction..................	-9,932,000	---	---
Sequester order..............	---	-10,768,000	---
Subtotal, adjusted appropriation............	744,152,000	832,977,000	886,875,000
Real transfer to OASH for AZT grants.................	-3,895,000	---	---
Comparative transfer to:			
Fogarty International Center for passport activity.................	-17,000	-17,000	---
Research Resources for administrative cost of RCMI program.............	-24,000	---	---
Comparative transfer from:			
Fogarty International Center for tropical diseases research center.	1,830,000	---	---
Office of the Director for additional FTEs......	1,824,000	---	---
Subtotal, adjusted budget authority.......	743,870,000	832,960,000	886,875,000
Unobligated balance lapsing..	-18,000	---	---
Total obligations.......	743,852,000	832,960,000	886,875,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1989 -- $6,595,000; 1990 -- $6,832,000; 1991 -- $7,119,000.

Excludes $12,000 for royalties received in 1989.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Budget Mechanism

(Dollars in thousands)

	1989 Actual		1990 Appropriation 1/		1991 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects						
Noncompeting	1,507	351,848	1,620	416,895	1,624	441,578
Admin. supplemental	(28)	1,602	(23)	1,081	(23)	1,117
Competing						
Renewal	240	49,974	175	43,582	213	47,463
New	402	62,643	293	54,831	357	60,580
Supplemental	10	1,150	8	802	10	1,250
Subtotal, competing	652	113,767	476	99,215	580	109,293
Subtotal, research projects	2,159	467,217	2,096	517,191	2,204	551,988
Research centers						
Specialized/comprehensive	26	19,840	28	19,865	28	19,865
Research Centers in Minority Institutions	--	1,859	--	1,834	--	1,834
Subtotal, research centers	26	21,699	28	21,699	28	21,699
Other research						
Research career program	93	5,428	101	6,057	101	6,057
Minority biomedical support	--	674	--	693	--	806
Other	69	4,160	67	4,040	67	4,040
Subtotal, other res	162	10,262	168	10,790	168	10,903
Total, research grants	2,347	499,178	2,292	549,680	2,400	584,590

Training						
Individual awards						
Noncompeting	66	1,765	92	2,504	53	1,488
Competing, new	28	781	39	1,084	78	2,045
Subtotal, individual	94	2,546	131	3,588	131	3,533
Institutional awards						
Noncompeting	373	9,226	401	10,539	457	12,007
Competing						
Renewal	75	1,711	92	2,135	54	1,218
New	37	959	46	1,286	28	735
Subtotal, institutional	485	11,896	539	13,960	539	13,960
Total, training	579	14,442	670	17,548	670	17,493
R&D contracts	158	101,357	163	117,519	172	126,515
	FTEs		FTEs		FTEs	
Intramural research	573	92,177	656	107,005	711	115,603
Research management and support	297	36,716	377	39,467	405	42,674
Extramural construction	--	---	--	1,796	--	---
TOTAL	870	743,870	1,033	833,015	1,116	886,875
HIV/AIDS	(229)	(312,888)	(306)	(393,958)	(343)	(423,407)

1/ Includes approximately $1,796,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

CROSSWALK - 1989 Actual

(Dollars in thousands)

PROGRAM ACTIVITY	MECHANISM: Research Grants: Research Projects	Research Grants: Research Centers	Research Grants: Other Research	Training Programs: Individual	Training Programs: Institutional	Research and Development Contracts	Intramural Research	Research Management and Support	Total
Allergy, immunology and transplantation..	$132,530	$9,149	$3,238	$1,150	$5,557	$3,833	...	...	$155,457
Microbiology and infectious diseases..	334,687	12,550	7,024	1,396	6,339	97,524	...	...	$459,520
Intramural research....	...	...	...	...	...	...	$92,177	...	$92,177
Research management and support..........	...	...	...	...	...	...	...	$36,716	$36,716
Total...............	467,217	21,699	10,262	2,546	11,896	101,357	92,177	36,716	743,870

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

CROSSWALK - 1990 Appropriation

(Dollars in thousands)

	MECHANISM									
	Research Grants			Training Programs						
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management and Support	Extramural Construction	Total
Allergy, immunology and transplantation..	$136,006	$8,976	$3,405	$1,640	$6,508	$3,719	---	---		$160,254
Microbiology and infectious diseases..	381,185	12,723	7,385	1,893	7,452	113,800	---	---		$524,438
Intramural research....	---	---	---	---	---	---	$107,005	---		$107,005
Research management and support..........	---	---	---	---	---	---	---	$39,467	---	$39,467
Extramural construction	---	---	---	---	---	---	---	---	$1,796	$1,796
Total...............	517,191	21,699	10,790	3,533	13,960	117,519	107,005	39,467	1,796	832,960

NOTE: Includes approximately $1,796,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

CROSSWALK - 1991 Estimate

(Dollars in thousands)

	MECHANISM								
	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management and Support	Total
PROGRAM ACTIVITY	Research Projects	Research Centers	Other Research	Individual	Institutional				
Allergy, immunology and transplantation..	$142,278	$8,976	$3,426	$1,640	$6,508	$4,432	---	---	$167,260
Microbiology and infectious diseases..	409,710	12,723	7,477	1,893	7,452	122,083	---	---	$561,338
Intramural research....	---	---	---	---	---	---	$115,603	---	$115,603
Research management and support..........	---	---	---	---	---	---	---	$42,674	$42,674
Total..............	551,988	21,699	10,903	3,533	13,960	126,515	115,603	42,674	886,875

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Summary of Changes

1990 Estimated budget authority	$832,960,000
1991 Estimated budget authority	886,875,000
Net change	+53,915,000

	1990 Current Estimate Base		Change from Base	
	Pos. (FTEs)	Budget Authority	Pos. (FTEs)	Budget Authority
Changes:				
A. Built-in:				
1. Within grade increase		$ 43,243,000		$ +528,000
2. Annualization of January 1990 pay raise (BID & SSF)		43,243,000		+412,000
3. January 1991 pay raise		43,243,000		+1,280,000
4. One extra day of pay		43,243,000		+176,000
5. Federal Employees Compensation Fund		145,000		+5,000
6. Unemployment compensation increase		69,000		+2,000
7. FTS rate increase		496,000		+18,000
8. Payment for centrally furnished services		30,278,000		+4,087,000
9. Service and supply fund increase		5,548,000		+242,000
10. Working Capital Fund		634,000		-29,000
11. Increased cost of laboratory materials and other supplies		64,556,000		+2,166,000
Subtotal				+8,887,000
B. Program:	No.	Amount	No.	Amount
1. Research projects:				
a) Noncompeting	1,620	417,976,000	+4	+24,719,000
b) Competing	476	99,215,000	+104	+10,078,000
Total	2,096	517,191,000	+108	+34,797,000
2. Other research	---	10,790,000	---	+113,000
3. R & D Contracts	163	117,519,000	+9	+8,996,000
4. Extramural construction		1,796,000		-1,796,000

Summary of Changes, continued

		Pos. (FTEs)	Budget Authority	Pos. (FTEs)	Budget Authority
5.	Research Management and support	377	39,467,000	+28	-146,000
6.	Intramural research	656	107,005,000	+55	+3,064,000
	Subtotal	1,033		+83	+45,028,000
	Total, changes . .				+53,915,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Budget Authority by Activity

(Dollars in thousands)

	1989 Actual		1990 Appropriation 1/		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Allergy, immunology, and transplantation.......	---	155,457	---	160,254	---	167,260
Microbiology and infectious diseases...	---	459,502	---	524,438	---	561,338
Intramural research.....	573	92,177	656	107,005	711	115,603
Research management and support...........	297	36,716	377	39,467	405	42,674
Extramural construction.	---	---	---	1,796	---	---
Total, Obligations.........	870	743,852	1,033	832,960	1,116	886,875
Unobligated balance, lapsing...............		18		---		---
Total, budget authority...........	870	743,870	1,033	832,960	1,116	886,875
HIV/AIDS	(229)	(312,888)	(306)	(393,958)	(343)	(423,407)

1/ Includes approximately $1,796,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

National Institute of Allergy and Infectious Diseases

Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Total number of full-time perm pos....	802	838	+36
Total compensable workyears:			
Full-time equivalent employment.....	1,051	1,134	+83
Full-time equivalent of overtime and holiday hours.................	14	14	---
Average ES salary....................	76,029	78,766	+2,737
Average GM/GS grade...................	9.5	9.5	---
Average GM/GS salary..................	34,181	35,377	+1,196
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207).	62,290	64,470	+2,180
Average salary of ungraded positions..	23,940	24,778	+838
Personnel compensation:			
Permanent positions.................	26,772,000	28,659,000	+1,887,000
Positions other than permanent......	8,685,000	8,910,000	+225,000
Other personnel compensation........	1,755,000	1,816,000	+61,000
Special personnel services..........	2,076,000	2,106,000	+30,000
Subtotal, personnel compensation..	39,288,000	41,491,000	+2,203,000
Personnel benefits....................	6,955,000	7,380,000	+425,000
Benefits for former personnel.........	67,000	69,000	+2,000
Travel and transportation of persons..	1,880,000	1,988,000	+108,000
Transportation of things..............	465,000	487,000	+22,000
Rent, communications and utilities....	3,065,000	3,157,000	+92,000
Printing and reproduction.............	514,000	569,000	+55,000
Other services:			
Project contracts...................	117,519,000	126,515,000	+8,996,000
Centrally furnished services........	30,278,000	34,365,000	+4,087,000
Standard level user charge..........	879,000	1,528,000	+649,000
Other...............................	37,039,000	34,386,000	-2,653,000

	1990 Appropriation	1991 Estimate	Increase or Decrease
Supplies and materials................	13,244,000	17,248,000	+4,004,000
Equipment............................	12,798,000	15,609,000	+2,811,000
Grants, subsidies & contributions.....	568,969,000	602,083,000	+33,114,000
Total.......................	832,960,000	886,875,000	+53,915,000

National Institute of Allergy and Infectious Diseases

Significant Items in the House and Senate Appropriations Committee Reports

Item	Action Taken or To Be Taken
1990 House Report	
Lyme Disease	
1. "This a newly recognized disease is the most common arthropod-borne disease in the United States, that is spreading rapidly across the U.S. .... The Committee urges the Institute to expand research in this critical area." (p.65)	1 . In order to stimulate research in the area of pathogenesis, which could result in improved treatment, more accurate diagnostic testing and development of an efficacious vaccine, and to expand NIAID support in this area, a Request for Applications (RFA) on the mechanisms of pathogenesis in Lyme borreliosis will be issued. It is anticipated that once final action is taken on the applications received support of Lyme borreliosis pathogenesis research will be more than double the current level of support in this area.
Sexually Transmitted Diseases	
2. "The Committee has stated repeatedly in years past, its support for increased STD research.....The Committee intends that studies be expanded to determine the role of STDs in the acquisition of HIV, and to determine the effect of HIV infection on the clinical manifestations of other STDs. The Committee is concerned about the serious health consequences of STDs, particularly for women and their babies. The Committee urges the NIAID to increase its efforts to stimulate more interest in STD research in areas not directly related to AIDS, as the Committee believes that such research efforts are currently inadequate to address these important diseases which have serious consequences for women, including infertility, ectopic pregnancy and cancer. Further,	2. The NIAID STD Branch, established in December 1988 to address the spiraling acute and chronic morbidity caused by STDs, is devoted entirely to the development and expansion of STD research. Through this Branch, the NIAID supports a large and growing portfolio of research grants, in all areas of STD research. The Institute also supports 8 program project grants for broadly-based STD Research Units, PID Research Units, and a Research Unit focused on the epidemiology of genital herpes. The Institute has major initiatives in research on human papillomavirus (HPV) infections, the development and use of rapid, accurate diagnostic tests for agents of

Item	Action Taken or To Be Taken
1990 House Report	
these diseases are now also implicated as risk factors for AIDS." (p.65/66)	clinical importance including STDs, plans to issue a request for applications for STD Cooperative Research Centers in the Spring of 1990. These Centers will provide a multi-disciplinary, systematic, sustained approach to STD research and will address and expand upon all the areas of interest expressed by the Committee. The NIAID has also organized five consensus-building conferences to address critical issues in STD research in 1989.
Social and Behavioral Research	
3. "The Committee encourages continued attention to the social and behavioral questions related to AIDS research throughout the National Institutes." (p.67)	3. Because AIDS is a preventable disease, behavioral research is an important component in many of the NIAID's AIDS activities. Nearly all natural history studies supported by the Institute include evaluation of the effectiveness of educational components designed to promote behavior change to reduce transmission. The recently initiated Community Programs for Clinical Research on AIDS by virtue of the patient population are intended to serve [e.g., intravenous drug users (IVDUs), minorities, etc.], will include the social, legal, and economic aspects of HIV infection particularly as it relates to compliance with the protocol regimens.
Hemophilia	
4. "The Committee is pleased to learn of NIAID's continuing commitment to improve access to clinical trials for hemophilia patients who suffer from AIDS, ARC or HIV infection. The Committee	4. The NIAID has a major contract with the National Hemophilia Foundation (NHF) to develop and implement a system of recruiting and following HIV infected persons with hemophilia in clinical trials to

Item	Action Taken or To Be Taken
1990 House Report	
understands that a working group comprised of hemophilia treatment centers' hematologists, NIAID scientists, and national hemophilia organization representatives are developing recommendations for expanding access beyond the AZT study to existing and new clinical trials covering the spectrum of infections from the asymptomatic phase to full-blown AIDS. Within the resources provided for the Institute, the Committee urges NIAID to increase its research support as appropriate, in order to expand experimental regimen options for hemophilia patients through the national hemophilia treatment network." (p.67/68)	evaluate potential AIDS therapies; and, to develop educational activities for persons with hemophilia, their spouses, and health professionals to increase their understanding of AIDS, HIV infection and methods of preventing HIV infection. NIAID staff met with the medical leadership of the NHF during their 1989 national meeting to discuss the future direction of the relationship between the NHF and the NIAID's AIDS Clinical Trials Group (ACTG). Plans are being formalized to extensively involve the NHF and its participating centers more fully in the ACTG effort, including scientific participation on its committees and in the protocol development process. It is expected that procedures will be put in place to allow broader access for the Hemophilia Network to ACTG protocols.
Chronic Fatigue Syndrome	
5. "The Committee commends the Institute for its intramural research progress on Chronic Fatigue Syndrome (CFS), and for its support for extramural CFS research. Substantial progress has been made in understanding CFS, but mush is still not known and the CFS research effort should therefore be broadened and expanded. To further extramural efforts, the Committee urges the NIAID to issue a Request for Applications on CFS in order to increase the number of extramural research grants funded. The Committee also urges the Institute to study the propriety and feasibility of establishing a research center for CFS study." (p. 68)	5. In the past three years, extramural research on CFS supported by NIAID has increased from 150 thousand dollars to more than half a million dollars in annual direct costs. Currently funded projects are concerned with natural history, selective immunologic defects in EBV immune responses in CFS, development of reagents to assess the role of herpes viruses, determination of laboratory markers which are prognostic or diagnostic, and estimation of prevalence in a population-based health maintenance organization. The NIAID will consider conducting a study, within its available resources, the propriety and feasibility of establishing a research center for CFS.

Item	Action Taken or To Be Taken
1990 House Report	
Vaccines	
6. "The Committee is aware of the crucial role of the development of vaccines in the prevention of disease and of the NIAID's commitment and leadership in this area. The Committee understands that major advances in basic research have opened the door for the development of novel approaches to vaccine development, such as recombinant DNA vaccines. These advances and new techniques offer promising research opportunities in several areas, including Lyme disease, pertussis, rotavirus, retroviruses, Group B streptococcal infection, and cytomegalovirus. The Committee would encourage the NIAID to intensify its vaccine development research efforts in these areas." (p.70)	6. The NIAID's broad research programs on all classes of infectious diseases and their causative agents, together with basic research on the immune system, have nourished a comprehensive, collaborative vaccine effort among scientists in government industry and academic institutions. New technology and knowledge gained from this research provide opportunities to resolve problems previously deemed insolvable. In setting priorities for vaccine development the NIAID weighs expected health benefits, projected net costs and feasibility given the current status of scientific knowledge about particular diseases and their causative agents. Further, as part of its program for accelerated vaccine development, the NIAID supports a network of Vaccine Evaluation Units to conduct early human trials of safety, immunogenicity, and protective efficacy of candidate vaccines. The Institute is considering the feasibility of or already conducting research and development of vaccines for the disease areas mentioned by the Committee.

Item	Actions Taken or To Be Taken
1990 Senate Report	
Lyme Disease	
1. "The Committee is concerned that Lyme Disease is spreading rapidly, with reported cases in 43 states and 21 nations around the world. Later manifestations of the disease are often debilitating .... The Committee expects $5,000,000 to be available for Lyme disease in FY 1990. The Committee expects that of this total $3,600,000 and $1,400,000 will be available for NIAID and NIAMS respectively." (p. 128)	1. NIAID conducts and supports basic research on Lyme Disease, addressing the biology of the causative organism of Lyme disease, the pathogenesis of the disease, diagnostic and protective antigens, and the host's immune response, as well as studying prevention and control of Lyme disease via research on vectors and reservoirs of the disease and their relationships to the causative agent and how it is transmitted among reservoirs, vectors and humans. In an effort to encourage and expand further research in these areas, the NIAID issued a Program Announcement and a Request for Application in FY 89. It is expected that NIAID FY 90 support of research in Lyme Disease will meet and perhaps exceed the $3.6 million level cited by the Committee.
Sexually Transmitted Diseases	
2. "The Committee intends that studies be expanded to determine the role of STDs in the acquisition of HIV, and to determine the effect of HIV infection on the clinical manifestations of other STDs. The Committee encourages the funding of cohort studies of the natural history of pelvic inflammatory disease. The Committee commends the Institute for initiating studies of the natural history of infection due to human papilloma viruses. The ultimate prevention of sexually transmitted diseases will be from the development of safe and effective vaccines, and the Committee encourages the Institute to continue supporting vaccine studies on all sexually transmitted diseases." (p.129)	2. The NIAID STD Branch, established in December 1988 to address the spiraling acute and chronic morbidity caused by STDs, is devoted entirely to the development and expansion of STD research. Through this Branch, the NIAID supports a large and growing portfolio of research grants, in all areas of STD research, and also . The Institute also supports 8 program project grants for broadly-based STD Research Units, PID Research Units, and a Research Unit focused on the epidemiology of genital herpes. The Institute has major initiatives in research on

Item 1990 Senate Report	Action Taken or To Be Taken
	human papillomavirus (HPV) infections, the development and use of rapid, accurate diagnostic tests for agents of clinical importance including STDs, plans to issue a request for applications for STD Cooperative Research Centers in the Spring of 1990. These Centers will provide a multi-disciplinary, systematic, sustained approach to STD research and will address and expand upon all the areas of interest expressed by the Committee. The NIAID has also organized five consensus-building conferences to address critical issues in STD research in 1989.
AIDS	
3. "The Committee has noted in the past concerns about the lack of opportunities for physicians and patients to participate in the evaluation of anti-HIV agents in many communities. The Committee is pleased that the Institute has initiated the community programs for clinical research on AIDS in fiscal year 1989, as Authorized in Public Law 100-607, and has created a special office to administer these contracts." (p.130)	3. In October 1989, the NIAID announced that a total of 18 community-based organizations in 14 cities had been awarded a CPCRA contract. These organizations are comprised of doctors and nurses working in a variety of settings who together, care for an aggregate of over 30,000 HIV-infected persons, a high percentage of whom are minorities, persons who use or have used IV drugs, women at risk, and gay and bisexual men. The CPCRA is seen as a pilot project in the delivery of administrative and methodologic support for community-based research and, at the same time, is designed to provide wider access to experimental therapies for HIV infection and its sequelae. Two CPCRA support contracts will be awarded in FY 90 for an Operations Center and a Statistical Center.
4. ".... The Committee has also expressed concern that the demographic diversity of those getting HIV infection is not reflected in the demographics of	4. The NIAID share's the Committee's concern regarding the demographics of those patients with HIV infection and their access to federally sponsored clinical trials

Item	Action Taken or To Be Taken
1990 Senate Report	
those participating in clinical trials. The Committee has therefore provided the administration's request to expand minority access the clinical trials funded by NIAID. The Committee urges the NIAID to assess the Institute's responsibility to support primary care associated with successful trial participation. In addition, the Committee requests the NIAID to develop with HRSA a plan to coordinate outreach for participation in clinical trials with those already funded to provide HIV-related primary care for minority and low income individuals, including community and migrant health centers and the maternal and child health programs.	programs. It is evident that new clinical research efforts should be concentrated to reach those populations that are presently underserved and the NIAID has undertaken several relevant new initiatives or activities targeting underserved populations including the Community Programs for Clinical Research on AIDS (CPCRA) - a new initiative that is designed to involve community physicians and their patients in clinical research. As part of its mission the CPCRA is intended to extend opportunities for participation in AIDS clinical research to underserved populations including minorities, intravenous drug users (IVDU), women, and, children. There are also several initiatives aimed at increasing the participation of minorities, women, and IVDUs in the NIAID AIDS Clinical Trials Group (ACTG) studies. To further address the needs of HIV infected children, the NIAID has expanded the number of both the Pediatric AIDS Clinical Trials Units it supports and pediatric studies conducted. The NIAID is exploring with HRSA the opportunities that might exist to try to link the ACTG studies with several of HRSA's HIV-related centers and programs addressing underserved populations.
5. ".... Within the increases provided, the Committee urges the NIAID to expand over the current level, experimental regimen options for hemophilia patients through the established national hemophilia treatment network." (p.131)	5. The NIAID has a major contract with the National Hemophilia Foundation (NHF) to develop and implement a system of recruiting and following HIV infected persons with hemophilia in clinical trials to evaluate potential AIDS therapies; and, to develop educational activities for persons with

Item	Action Taken or To Be Taken
1990 Senate Report	
	hemophilia, their spouses, and health professionals to increase their understanding of AIDS, HIV infection and methods of preventing HIV infection. NIAID staff met with the medical leadership of the NHF during their 1989 national meeting to discuss the future direction of the relationship between the NHF and the NIAID's AIDS Clinical Trials Group (ACTG). Plans are being formalized to extensively involve the NHF and its participating centers more fully in the ACTG effort, including scientific participation on its committees and in the protocol development process. It is expected that procedures will be put in place to allow broader access for the Hemophilia Network to ACTG protocols.
Vaccine Development	
6. "The Committee is aware of the crucial role of the development of vaccines in the prevention of many diseases and of NIAID's commitment and leadership in this area. We have heard from many individuals that major advances in basic research have opened the door for the development of novel approaches to vaccine development, such as recombinant DNA vaccines. In that regard, the Committee hopes that the Institute will place on its list of priorities vaccine development for the following: Lyme disease, because of its increasing incidence and difficulties in preventing tick bites; pertussis, a common cause of childhood bacterial infection; rotavirus, the most common cause of infant mortality; HTLV I/II retroviruses which are transmitted through blood and blood products; group B streptococcal infection, a devastating bacterial infection of	6. The NIAID's broad research programs on all classes of infectious diseases and their causative agents, together with basic research on the immune system, have nourished a comprehensive, collaborative vaccine effort among scientists in government industry and academic institutions. New technology and knowledge gained from this research provide opportunities to resolve problems previously deemed insolvable. In setting priorities for vaccine development the NIAID weighs expected health benefits, projected net costs and feasibility given the current status of scientific knowledge about particular diseases and their causative agents. Further, as part of its program for accelerated vaccine development, the NIAID supports a network of Vaccine Evaluation Units to conduct early human trials of safety,

Item	Action Taken or To Be Taken
1990 Senate Report	
newborn infants and common cause of mental retardation; and cytomegalovirus a virus transmitted from mothers to their infants which has been known to cause birth defects." (p. 131/132)	immunogenicity, and protective efficacy of candidate vaccines. The Institute is considering the feasibility of or already conducting research and development of vaccines for the disease areas mentioned by the Committee.
Tuberculosis	
7. " ....The Committee encourages the NIAID to coordinate its activities with other PHS agencies that are implementing the strategic plan to eliminate tuberculosis." (p.132)	7. The NIAID continues to place a major emphasis on the development of new and improved vaccines and diagnostic tests for TB, as well as the development and screening of drugs that will be more effective and less toxic in the treatment of TB. The NIAID coordinates it efforts in this area of research with other expert PHS Agency and non-government scientists by serving on the PHS Task Force on the Elimination of Tuberculosis, as well as the Committee on Priorities for Tuberculosis Research.
Brown Tree Snakes	
8. "The Committee has become aware of the infestation of Guam with the brown tree snakes. The Committee directs NIAID to work with the public health authorities to ensure that the necessary anti-brown tree snake venom is developed and made available to the residents of Guam in a timely fashion." (p. 132)	8. The NIAID has had extensive interactions with the office of Senator Inouye of Hawaii on the problem of brown tree snake infestation. Subsequent to these interactions the NIAID has identified, communicated with, and coordinated interactions among: an extramural research scientist who has been concerned with the study of the treatment of poisonous snake bites and her colleagues; two NIH intramural scientists studying aspects of the brown tree snake that may be useful in capturing and controlling their infestation; and various authorities from the Department of Interior (US Fish and Wildlife), the office of the PHS Pacific Basin Regional Health Administrator, and appropriate Government and non-government public

Item	Action Taken or To Be Taken
1990 Senate Report	
	health entities in Guam. These discussions are focusing on determining the necessity of as well as the scientific means to develop an antivenom for clinical use, and identifying the support necessary to conduct these studies.
Chronic Fatigue Syndrome	
9. ".... The Committee understands that many patients who believe they have essentially recovered or who are in whole or partial remission from the most severe symptoms of CFS are finding that they have very weak and damaged immune systems that are very susceptible to other disease. The Committee recommends research on understanding and correcting the immune system damage associated with CFS. The Committee also suggests that the NIAID study the establishment of a research center for CFS studies including collecting and analyzing of clinical and laboratory data on patients." (p. 132/133)	9. Research on the immune system and its functions in the maintenance of health and its malfunctions in the production of disease is an integral part of the NIAID mission, and is the cornerstone of NIAID research on CFS. The NIAID will consider, within its available resources, the propriety and feasibility of establishing a CFS research center.
Nursing	
10. "The Committee is most pleased to learn that the NIAID AIDS Program has hired a number of individuals with nursing backgrounds and placed them in vital data coordinator, health specialist, and program analyst positions, and that NIAID included nurses on its Minority Ad Hoc Advisory Committee which met in May 1988 to develop recommendations on AIDS activities to the NIAID Director.... The Committee urges the NIAID to continue its efforts to involve nurse researchers in its activities and programs." (p. 133)	10. The NIAID recognizes the vital role that nursing professionals play in our research efforts. This recognition is particularly highlighted when focusing on NIAID's research programs on AIDS. Nurses working on NIAID intramural AIDS studies act as both principle investigators and perform independent research activities that transcend the traditional nursing support function. Such integral and independent nursing roles have also been identified in other NIAID extramurally supported programs. In addition, the NIAID has employed

Item	Action Taken or To Be Taken
1990 Senate Report	
	individuals with nursing backgrounds in a variety of essential AIDS Program and institute-wide positions. Nurses are also included on a number of NIAID ad hoc and chartered committees and are addressed as the principle audience in a number of NIAID publications and outreach and technology transfer activities. The NIAID plans to continue with its ongoing efforts to involve members of the nursing community in prominent roles that transcend the traditional nursing support function.
Immunology Research 11. "The Committee has heard from numerous witnesses regarding the role of the immune system and the need for further research in HIV infection, cancer, immunologically based diseases, transplantation, viral and bacterial infection ..... With this in mind, the Committee expects the NIAID to continue to strengthen its basic research programs in immunology. (p.133)	11. NIAID supports studies in basic immunology concerned with the properties, interactions and functions of the cells of the immune system and the products elaborated by those cells. Recognizing that the information gleaned from fundamental, untargetted research is the raw material from which clinical stratagems and biotechnical applications are fashioned, the NIAID supports a broad range of research concerned with basic structure and function of the immune system. In addition, the NIAID supports Program Projects on the Biology of the Immune System, which focus upon the biologic and chemical structure of the immune system to help understand the basic cellular and molecular immune responses in health and disease.

Item	Action Taken or To Be Taken
1990 Senate Report	
12. " The Committee recognizes the increasing role of the environment on diseases such as allergies and asthma.... The Committee is therefore interested in the NIAID conducting further research in this important area." (p. 133)	12. NIAID promotes the interaction of basic and clinical scientists by supporting specialized Asthma and Allergic Disease Centers which conduct research on the causes, prevention, and treatment of these disorders. Centers encourage collaborative studies among immunologists, geneticists, biochemists, pharmacologists and clinicians.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1990 Amt. Authorized	1990 Appropriation	1991 Amt. Authorized	1991 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$815,467,000	Indefinite	$869,382,000
National Institute of Allergy and Infectious Diseases	Section 446	42§285f	Indefinite		Indefinite	
National Research Service Awards	Section 487	42§288 -1	Such sums as 1/ necessary	17,493,000	Authorizing 1/ legislation to be requested	17,493,000
Total Budget Authority..........				832,960,000		886,875,000

1/ This training authority is shared with other research training programs of the National Institutes of Health, and the Alcohol, Drug Abuse and Mental Health Administration.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1982	214,504,000 2/	259,763,000	246,452,000	235,895,000
1983	246,043,000	276,367,000	270,795,000	279,122,000
1984	289,428,000	307,128,000 3/	304,228,000 3/	317,663,000
1985	325,379,000	355,728,000 4/	375,091,000	368,528,000
1986	366,964,000	355,453,000 5/	412,965,000	366,964,000
1986 Sequester				-16,488,000
1987 6/	330,551,000	403,853,000	541,343,000	545,523,000
1988	551,102,000	439,667,000 7/	661,458,000	638,800,000
1989	435,084,000 8/	732,453,000 9/	758,352,000	744,152,000
1990	442,596,000 10/	845,523,000	847,112,000	843,745,000 11/
1990 Sequester				-10,768,000
1991	886,875,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Reflects the September amendment; the original request was $243,755,000

3/ Excludes $8,619,000 in NRSA training programs not considered.

4/ Excludes $8,690,000 in NRSA training programs not considered.

5/ Excludes $11,382,000 in NRSA training programs not considered.

6/ The budget estimate to Congress proposed that all funding for AIDS research be consolidated in the Office of the Assistant Secretary for Health. The House consolidated all NIH AIDS funding in the Office of the Director, NIH; the Senate allowance and appropriation spread the funding among the Institutes, including $145,850,000 for NIAID.

7/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

8/ The 1989 request excludes funds for AIDS research ($310,268,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

9/ Excludes $13,537,000 in NRSA training programs not considered.

10/ The 1990 request excludes funds for the National HIV program ($400,116,000) proposed for consolidation in the Office of the Assistant Secretary for Health.

11/ Excludes enacted administrative reduction of $2,573,000.

Justification

National Institute of Allergy and Infectious Diseases

	1990 Estimate		1991 Estimate		Increase or Decrease	
	FTE	BA	FTE	BA	FTE	BA
TOTAL....	1,033	$832,960.000	1,116	$886,875,000	+83	+$53,915,000
AIDS.....	(306)	(393,958,000)	(343)	(423,407,000)	(+37)	(+29,449,000)

General Statement

The National Institute of Allergy and Infectious Diseases (NIAID) stands at the forefront of scientific research on a wide range of diseases that affect the quality of life of millions of people in the United States and other countries. NIAID's mission is to conduct and support research and training that will improve the Nation's ability to prevent and control infectious diseases and diseases that result from disorders of the immune system. To accomplish this goal, NIAID conducts basic, applied, and clinical investigations in its intramural laboratories at Bethesda, Rockville, and Frederick, Maryland, and Hamilton, Montana, and supports research and training at many universities and medical centers in the United States. The Institute's activities are carried out by its four major divisions: the Microbiology and Infectious Diseases Division, the Allergy, Immunology, and Transplantion Division, and the Acquired Immunodeficiency Syndrome Division, which comprise the extramural program, and the Division of Intramural Research whose research spans the entire spectrum of NIAID's mission.

The Institute's research projects combine various related disciplines, including virology, parasitology, bacteriology, mycology, molecular biology, immunobiology, immunochemistry, immunoregulation, immunogenetics, transplantation biology, and immunopathology. Because of NIAID's distinguished role in studies of the immune system and infectious diseases, it has the lead responsibility within the National Institutes of Health (NIH) for conducting basic and clinical research on the acquired immunodeficiency syndrome (AIDS). The rapid advances in AIDS research are contributing significantly to the scientific base of knowledge about other immune system disorders, infectious diseases, and certain neoplasms.

Exciting discoveries by NIAID-funded researchers over the last year have built on the decades of outstanding basic research that has provided the foundation for this nation's immediate response to public health emergencies such as AIDS. Research highlights include:

NIAID supported researchers at Tulane University reported that they protected eight of nine monkeys against simian AIDS, an AIDS-like virus in monkeys, with a vaccine. The Simian Immunosuppressive Virus (SIV) is killed so it does not infect its hosts and is then injected into monkeys so their immune system may respond and build up its natural defenses against invasion by a live virus. Development of Simian AIDS vaccine holds great potential for the development of a vaccine for humans. These studies are unambiguous proof that a vaccine for human AIDS is possible.

The NIAID azothymidine (AZT) Protocols 016/019 proved that AZT was effective at the earlier stages of AIDS and as a result, the number of recipients that may benefit from AZT will be increased.

Advances in the use of animal models is providing many benefits in areas such as perinatal transmission of the AIDS virus. The number of infants infected with HIV transmitted from the mother is a growing health problem and the method and time of transmission of the AIDS virus from mother to child is not known. A mouse model has been developed to test the capacity of drugs to stop the transmission of HIV from mother to child before or at birth.

In the sexual transmission of the AIDS Virus it has been found that HIV will multiply and cause disease only in humans. Researchers have been successful in developing a methodology by which SIV is transmitted through the genitalia into the bloodstream. This procedure provides the only animal model of sexual transmission of the HIV virus.

Several experimental AIDS drugs have emerged from the National Cooperative Drug Discovery Groups (NCDDG) program and have entered clinical trials: sCD4, d4T and AZU.

The Community Programs for Clinical Research on AIDS expanded access to patients who previously were unable to participate in clinical trials. This program will enable us to include patients that represent extraordinary geographic, racial and risk groups in our trials.

There have also been many advances in our Immunology and Infectious Diseases excluding AIDS programs. For example, only about 60-70 percent of people with Lyme disease develop easily recognizable symptoms. A major roadblock to effective treatment of Lyme disease has been the lack of reliable tests to diagnose the disease during early infection. NIAID scientists at Rocky Mountain Laboratories have developed a process utilizing the polymerase chain reaction (PCR) that locates and repeatedly duplicates the disease-causing bacterium, making the presence of the infectious agent overwhelmingly obvious and thereby identifiable. With this unique process, as little as five or fewer organisms can be detected within a sample, significantly increasing the possibility of an early and accurate diagnosis. As a result, NIAID researchers using this PCR process have developed a potentially more effective diagnostic test for Lyme disease.

The current whole cell vaccine for pertussis, which has been in use since 1945, is 70-90 percent effective and has reduced the incidence of pertussis by 99 percent. However, this vaccine is associated with high rates of adverse reactions, which have led to many lawsuits. A variety of new, acellular pertussis vaccines have been developed which are expected to be less reactogenic and the NIAID has been actively involved in the evaluation of new pertussis vaccines.

The prevalence rate of childhood asthma is increasing as have related hospitalizations, especially among urban minorities. Approximately 40,000,000

Americans suffer from allergic diseases. Ten million of these have asthma, one third of whom are under 18 years of age. Urban asthma clinical trials have been started and hopefully will produce treatment methodologies that will help alleviate this growing problem.

Overall Budget Policy

The FY 1991 budget request for NIAID stresses basic research and totals $886,875,000, an increase of $53,915,000 or 6.5 percent from the comparable FY 1990 level of $832,960,000. This request includes $423,407,000 for AIDS which is a seven percent increase over the FY 1990 level of $393,958,000. The Institute will direct 66 percent of its extramural research funds in support of research grants.

In FY 1991, the request will support a total of 2,204 research project grants compared to 2,096 in FY 1990. Included in the total are 1,624 noncompeting research project grants and 580 competing research project grants compared to 1,620 and 476 respectively, in FY 1990. On average, noncompeting grants will receive an average increase of about 5.7 percent.

The FY 1991 request includes funding for 28 research centers and will be funded at the same level as FY 1990. Funds for other research will allow NIAID to make 101 awards which is the same level as FY 1990. MBRS awards will receive an increase of 16 percent over FY 1990; and other research grants will be funded at the same level as FY 1990.

The number of full-time training positions to be supported will remain the same as in FY 1990 for a total of 670. The current policies on the payment of indirect costs and institutional allowances will be continued in FY 1991.

The FY 1991 request provides $126,515,000 for R&D contracts compared to $117,519,000 in FY 1990. Included in this amount is a program increase of $4 million for the first year cost of a pertussis clinical trial and funds for basic research on a new candidate pertussis vaccine.

Support for intramural research and research management and support in FY 1990 are $115,603,000 and $42,674,000, respectively. The FY 1991 levels reflect built-in increases and a program increase for intramural research. The increases in intramural research and research management and support will provide support for 55 and 28 additional FTE's respectively.

Program Accomplishments

Basic research in immunology provides the fundamental information that is the essential raw-material from which to fabricate clinical tools and procedures. Without a vigorous program in basic research, advances in diagnosis, treatment and prevention of human diseases would be slow, indeed, and in many instances impossible. Therefore, the NIAID takes pride in its encouragement and support of many vigorous laboratories dedicated to fundamental research in immunology.

Allergy

Recent statistics show that approximately 40,000,000 Americans suffer from allergic diseases. Various types of allergic disease are under investigation, including: immediate-type hypersensitivity and its disorders, e.g. allergic rhinitis, atopic dermatitis, urticaria and angioedema; allergic reactions caused by insect stings, foods, airborne allergens and infectious agents; manifestations of delayed hypersensitivity and contact dermatitis; drug reactions; and chemical sensitization.

Important, new information on cytokines was discovered in the function of allergy and inflammation during the last year. A NIAID grantee has recently demonstrated that the cytokine, transforming growth factor beta-1, can inhibit the growth of mast cells (cells in tissues having a specific recognition unit for IgE) without affecting either their function or differentiation. An understanding of cytokine function will lead to a better understanding of the mechanisms that underlie allergic and inflammatory diseases.

Patients with skin rashes associated with food allergies have been shown to exhibit high spontaneous release of the mediator, histamine, *in vitro* from their basophils. Grantees have now demonstrated that these patients spontaneously produce a cytokine, histamine releasing factor (HRF), in their mononuclear blood cells and that these individuals have a unique form of IgE (IgE^+) in their serum that allow their basophils to respond to histamine. This unique IgE^+ is not present in the serum of patents with rashes who are not allergic to food. These factors may play an important role in sustained continual degranulation of mast cells in the skin leading to the pathogenic changes that are seen.

Asthma

Recent statistics show that approximately 40,000,000 Americans suffer from allergic diseases. Ten million of these have asthma, one third of whom are under 18 years of age. The prevalence rate of childhood asthma is increasing as have hospitalizations, especially among urban minorities. Data also indicate an increase in mortality from asthma, particularly among individuals over the age of 65.

The chronic natures of asthma and rhinitis are the subject of intense study. Studies comparing the chemicals and cells point to the basophil as playing a key role in causing the late phase response.

The eosinophil is a type of white blood cell formerly thought to be associated with allergic reactions in a "mop up" role. The eosinophil is now thought to play a primary role in allergic reactions. Eosinophil-derived products are now known to be capable of causing sloughing of the lining of the lung, bronchoconstriction, and are thought to be responsible for the recognizing and processing of foreign substances.

Genetics and Autoimmune Diseases

Autoimmune diseases are characterized by aberrations in the immune system resulting in the development of antibodies and cells which react with self components leading to the development of clinical diseases, including: systemic lupus erythematosus, myasthenia gravis and diabetes. Our understanding of immunologic diseases has been advanced by recent developments in molecular immunology.

One approach to the treatment of Multiple Sclerosis (MS) would be to use synthetic molecules to block the immune system or misdirect it away from myelin. In studies supported by NIAID, investigators have now characterized the sites on MHC class II molecules which are important for the response to a portion of myelin basic protein. These studies have yielded the information required for the construction of synthetic molecules which then in turn can be used to block the immune response to myelin.

One therapeutic approach to Insulin Dependent Diabetes Mellitus (IDDM) is to prevent the destruction of the insulin producing beta islet cells using immunosuppression. In order to make this feasible, it is necessary to be able to accurately diagnose those individuals who will develop IDDM. In studies supported by NIAID, investigators have now used an advanced and rapid molecular technique called allele specific oligonucleotide (ASO) analysis to type large populations of normal individuals and patients with IDDM. The conduction of these studies have led to the improvement of the accuracy of assessment of susceptibility to IDDM and have provided clues as to the nature of the molecules which are the target of the destructive immune response.

Genetics and Transplantation Biology and Organ Transplantation

A fundamental objective of the research in this area is to stimulate the development of interventions in the immune response to foreign tissues based on a detailed understanding of the biology of the immune system.

Immune effector cells responsible for the rejection of transplanted organs express a receptor for the T-lymphocyte growth factor, interleukin-2 (IL-2). In studies supported by the NIAID, researchers have utilized a monoclonal antibody to the IL-2 receptor (IL-2R) to treat recipients of cadaveric kidney transplants during the initial weeks following transplantation. This form of immunotherapy reduces the number of rejection episodes during the initial post-transplant period and delays the time to the first rejection episode. Investigators have succeeded in inducing an acquired immune tolerance in kidney transplant patients with total lymphoid irradiation prior to transplantation. These investigators have shown that this pretreatment regimen permitted the withdrawal of standard immunosuppressive drugs from three patients who were experiencing serious side effects to these drugs, azathioprine or steroids, without prejudicing the survival of the kidney transplant. This represents the first documented incidence of transplantation tolerance in humans.

Bone Marrow Transplantation

Bone marrow transplantation has become an accepted therapeutic procedure for the treatment of a variety of fatal diseases, such as severe combined immunodeficiency disease, aplastic anemia, and leukemia. However, bone marrow transplantation differs substantially from the transplantation of organs such as kidney or heart, in that bone marrow contains lymphoid cells which may attack the recipient leading to graft-vs-host disease (GVHD). The development of GVHD leads to an increased risk of infectious complications following transplantation and in severe cases can be fatal.

Lymphokines are proteins secreted by T-lymphocytes following interaction with antigens and can either enhance or suppress the immune system. Investigators have produced several monoclonal antibodies to the lymphokines - interferon-gamma and tumor necrosis factor. Using these antibodies, they were able to reverse the immune dysfunction associated with GVHD following bone marrow transplantation, indicating that interferon-gamma and tumor necrosis factor may play prominent roles in the pathogenesis associated with this disease.

Recent breakthroughs in modern recombinant DNA and gene cloning techniques, and methodologies for introducing genes into cells, have provided the tools for the development of new treatment regimens for specific single-gene hereditary defects. This methodology in conjunction with bone marrow transplantation may provide a "cure" for genetic disorders of hematopoietic precursor cells within the bone marrow, i.e., thalassemia and a severe combined immunodeficiency disease which is due to a defective gene for the enzyme adenosine deaminase.

Occupational Lung Disease

Among the many types of occupational lung diseases are a group known as occupational immunologic lung diseases (OILD), which include the syndromes of allergic asthma and hypersensitivity pneumonitis or allergic pneumonia. The exact magnitude of these problems is unknown, but as many as 15 percent of workers in some industries are affected. At risk workers include the eight million Americans living on farms who may develop hypersensitivity pneumonitis from exposure to moldy hay. In addition, 200,000 grain workers are exposed to grain dust inhalation. Another 90,000 workers contacting animals through veterinary science, animal handling, and laboratory research may develop allergic asthma in response to these exposures. OILD can also result from occupational exposure to food allergens, and affect unknown millions of Americans including homemakers.

A NIAID funded researcher has developed a new immuno-assay, that is able to differentiate symptomatic from asymptomatic workers with the same exposures and holds promise as a reliable diagnostic technique.

Isocyanates are used in the manufacture of many products including insulation, foam fillings, and polyurethane paints. Both toxic and allergic reactions of the nose, eyes, and lungs have resulted from isocyanate exposures. Prospective studies of isocyanate exposure of workers have given leads as to the safe human levels of this chemical.

Bacterial Vaccines Program

A main goal of the Bacterial Vaccines Program is to develop safe and effective vaccines for the prevention of bacterial diseases. A major emphasis is the immunological response of infants, the elderly, and various high-risk groups. Examples of current vaccine development and testing relate to the following disease categories: pneumonia, otitis media, meningitis, bacteremia, whooping cough, and neonatal sepsis.

NIAID continues to test a new generation of meningitis vaccines designed to protect infants. These candidate vaccines involve the coupling of bacterial polysaccharide components with other antigens i.e., carrier proteins. Clinical trials are in progress to test the safety and immunogenicity of these new vaccines in infants.

Two areas of research starting to receive more attention include Neisseria meningitidis and group B streptococcal disease. For both these organisms, the major research efforts and areas of accomplishment have been in better understanding the roles of both bacterial and host factors in the pathogenesis of infections caused by these two pathogens. The development of vaccines has also been a high priority, and much progress has been made toward developing a group B streptococcal and meningococcal A, B, and C conjugate vaccines and testing for the induction of functional antibody. In addition, anti-idiotype meningococcal vaccines have been developed and are now being tested in animals for the production of functional antibody.

Lyme disease

Lyme disease is the most common vector-borne disease of bacterial etiology in the United States and Europe. National estimates suggest that approximately 5,000 cases occurred in 1988 in at least forty-three states. Most experts agree that this estimate is low by at least a factor of two, the Lyme Borreliosis Foundation believes that the actual number of new cases is over 50,000. The disease is primarily transmitted to humans and other animals by one or more species of ticks. However, deer and rodents appear to be the most important reservoirs. The etiologic agent of Lyme disease is a spirochete, Borrelia burgdorferi. Although the etiologic agent has been isolated and cultured in the laboratory, and is exquisitely sensitive to antibiotics in vitro, Lyme disease has proven to be a difficult bacterial infection to diagnose and treat. The most recent accomplishment on this disease was research achieved at the NIAID Rocky Mountain intramural laboratories and focused on studies that should result in improved diagnostic tools. Studies on antigen expression and genetic variability in Borrelia burgdorferi are in progress. Efforts to develop an improved method of detecting Borrelia burgdorferi in clinical specimens utilizing the polymerase chain reaction are continuing.

Hepatitis

There are over 600,000 new viral hepatitis infections each year in the U.S. - 25 percent hepatitis A virus (HAV), 50 percent hepatitis B virus (HBV), and 25 percent non-A, non-B hepatitis (NANB). At least two forms of NANB exist; the predominant form in the U.S. is post-transfusion NANB (PTNANB) whose newly proposed name is hepatitis C virus (HCV). Licensed HBV vaccines prevent infection but are under utilized due to their expense. Thus, the number of HBV cases/carriers continues to rise. No treatments are available for cure or amelioration of HBV, hepatitis delta virus (HDV) and PTNANB chronic disease. Methods of preventing HAV or NANB hepatitis are not available.

NIAID grantees have identified processes in HBV's growth cycle which may serve as targets for antiviral drugs. For example, polymerase, reverse transcriptase, protease, receptors, RNA subspecies and regulatory elements can all be targeted.

NIAID-supported investigators have developed several tissue culture systems and animal models with which to study HBV and other hepadnaviruses. These are useful for basic research as well as evaluation of antiviral drugs.

Accelerated Development of Vaccines

Vaccines represent the most cost-effective approach to the prevention of serious disease developed to date. Moreover, during the last two decades the world has witnessed a revolution in biological and medical science. This revolution has greatly expanded our knowledge of basic immunology, infectious disease, epidemiology and pathogenesis. In addition, a number of practical innovations, such as monoclonal antibody and recombinant DNA technologies have been introduced that greatly facilitate and expand our ability to do research in biology in general, but particularly on vaccines. This combination of factors raises the prospect that if resources can be focused on the accelerated development of vaccines, many new vaccines will be developed and thereby enhance our capacity to control infectious diseases that currently are not preventable by vaccination.

Haemophilus influenzae type B polysaccharide vaccine conjugates have been developed that show great promise in immunizing young infants. Clinical trials of these new conjugate vaccines are soon to be completed and we anticipate that they will be very effective in protecting children from this infection which causes significant mortality and morbidity.

Pneumococcal polysaccharide conjugated vaccines have been developed which also show promise. These vaccines will enter clinical evaluation probably within the next year. If these vaccines are shown to be safe and effective they will greatly reduce the incidence of pneumococcal disease in infants and also help control otitis media.

Candidate conjugate vaccines for prevention of Group B streptococcal (GBS) sepsis in infants have also been developed. This disease is most devastating in its impact on infants during the first few months of their lives. Accordingly, this vaccine will be given to pregnant mother's before delivery to augment the degree of passive immunity in the newborn and thereby prevent the disease.

A new cholera vaccine candidate has been developed that shows great promise. This vaccine, CVD103HgR, is a living Vibrio cholera that is attenuated due to changes introduced into the cholera toxin that make it non-toxic. This vaccine entered phase 1 clinical trials this year.

A cold-adapted vaccine for parainfluenza type 3 has been developed and is proposed to enter clinical evaluation in the near future.

Two candidate malaria circumsporozoite vaccines entered clinical evaluation this year.

The use of virus vectors as an approach to immunization reached an important milestone last year with the first clinical trials of a vaccinia-vectored HIV glycoprotein vaccine. Other promising vectored vaccines include the use of adenovirus-HIV, adenovirus-HBV, poliovirus-chlamydia and salmonella-circumsporozoite.

Clinical trials of two herpes virus type 2 candidate vaccines were initiated last year. One of these vaccines is an attenuated HSV2 virus, while the other consists of purified viral glycoproteins.

Haemophilus Influenzae type B

Haemophilus influenzae type b (Hib) remains the major cause of invasive bacterial disease and meningitis in children under five years of age. Protection against invasive disease by immunization with the capsular polysaccharide (PRP) has been moderately successful in children over two years of age. Response to the PRP vaccine in children less than two years is minimal or absent. Similarly, immunologic response to invasive Hib disease in this age group is minimal, or at best, unpredictable.

Children recovering from a bout of invasive Hib disease are able to demonstrate a significant antibody response following the administration of Hib conjugate vaccines as compared to a much lower response in children who were treated with a capsular polysaccharide vaccine. The responses were considered protective and equivalent to the type of responses observed in normal children of the same age receiving the identical conjugate vaccine.

Children recovering from Hib disease who did not respond initially to a polysaccharide vaccine, did so following the subsequent administration of a conjugate Hib vaccine. These data show that children recovering from invasive H. influenzae type b disease (i.e. meningitis) can be successfully immunized against recurrent episodes of infection and that they are not immunologically deficient (tolerant) or incapable of responding to haemophilus antigens on the cell surface. This observation bodes well for the efficacy of new Hib conjugate vaccines in high risk children.

Otitis media (OM) is caused by numerous and diverse bacterial species. Streptococcus pneumonia and non-typable Haemophilus influenzae are the leading cause of OM. Molecular biology approaches have been used to develop a non-typable Haemophilus influenzae vaccine component. Scientists have isolated the bacterial genes and cloned them to produce bacterial proteins in sufficient quantities to identify which ones may be useful in infant rat animal protection studies. They have identified at least three minor bacterial surface proteins having a strong potential for vaccine use, especially as carriers.

A new method has been developed to prevent meningitis and other life threatening infections in young infants whose immune systems are too immature to respond to available vaccines. The method involves the administration of protective antibodies purified from the plasma of adults who have been immunized with these vaccine. The antibody preparation is call BPIG.

Parasitic Diseases

Parasitic diseases continue to plague literally billions of people in the modern world, killing millions annually and inflicting debilitating injuries such as blindness and disfiguration on additional millions. In addition, parasites remain a public health concern within the U.S. Many human parasites are widely distributed in this country, but remain subclinical because of other influences such as good nutrition and hygiene practices. However, symptomatic parasitic infections are becoming more widely observed here with increasing travel of U.S. citizens abroad and immigration of people from third world areas. In immunologically immature or immunosuppressed populations, parasitic infections represent a significant cause of morbidity or mortality.

Continued application of new biotechnology has led to scientific advances in the areas of diagnosis, chemotherapy, vaccine development, immunopathology and immunoregulation of parasitic diseases, and vector biology. Specific examples include the identification of molecular probes to distinguish pathogenic and non-pathogenic forms of the filarial parasite that can cause river blindness, a discovery that will lead to more efficacious use of targeted drug delivery and vector control programs.

Potential vaccine immunogens for malaria, schistosomiasis, filariasis and amoebiasis have been identified and are being tested in animal models. These include antigens that may induce protective immunity against the infectious or invasive stages of the parasites and/or that may block transmission of the parasite by its vector.

Genetic transformation of the protozoal parasites, trypanosomes and leishmania, as well as of mosquitoes is leading to increased understanding of the molecular mechanisms of gene expression in these organisms, and could pave the way for development of innovative new control measures.

Pertussis

Although the present whole pertussis vaccine has been effective in protecting children from pertussis disease and is well accepted in the United States, undesirable side reactions to the vaccine have been observed. Local and mild reactions such as fever, pain and swelling occur frequently. Rarely, more serious reactions (i.e., convulsions, encephalopathy) occur. Concern about these adverse reactions have caused a dramatic decrease in the acceptance of the vaccine in countries such as the United Kingdom and Sweden, and in this country has become a very sensitive issue in the minds of many parents and health advocates. Accordingly, it will be necessary to perform clinical trials for any new acellular pertussis vaccines to show that they actually prevent pertussis effectively in infants and are at least as good as the conventional whole cell vaccine when administered as a three dose regimen.

Since B. pertussis adheres to and causes disease at mucosal surfaces mucosal immunity may be more effective than serum antibodies from an injected vaccine. In recent experiments, oral infection of mice with such a vaccine resulted in the production of serum and mucosal antibody against a B. pertussis protein.

Genetic engineering has been used to construct a live attenuated vaccine strain of Salmonella which produces nontoxic B. pertussis surface components. Attenuated Salmonella vaccine vectors cause a very mild intestinal infection, and coincidentally confer immunity to Salmonella intestinal infections. Such a recombinant vaccine would, like the Sabin polio vaccine, be fed to children rather than injected.

Tropical Disease

Tropical diseases are the major health problem in those geographic areas where much of the world's population lives. The establishment and maintenance of research units in tropical infectious diseases where research can be carried out on these problems is essential if progress is to be made in controlling or reducing the impact of tropical diseases. In addition, the availability of research units of this type make it possible for U.S. investigators to receive experience and training which is otherwise not available. This is particularly important in view of the fact that approximately 12 million U.S. citizens travel to the regions of the globe where these infections are endemic each year. NIAID supports, in addition to investigator-initiated research grants, two programs which support tropical disease research--Tropical Disease Research Units and The International Collaboration in Infectious Disease Research program. Major advances have been made within these programs in the fields of malaria, leishmaniasis, onchocerciasis and schistosomiasis.

Molecular biologic studies have shown that Plasmodium falciparum contains at least two genes related to the mammalian multiple drug resistance genes, and at least one of which is present in higher copy number in a drug resistant strain than in a drug-sensitive one. This suggests that drug resistance in malaria parasites could be similar to that of drug resistant mammalian cells and could lead to new strategies for chemotherapy against drug resistant strains of malaria.

A large scale clinical trial to assess the usefulness of nucleic acid hybridization for the diagnosis of cutaneous leishmaniasis in an endemic area of Brazil has shown that this approach is more sensitive than direct examination.

Pneumonia

Pneumonia is the most serious acute disease of the respiratory system. It is a clinical condition which can be caused by a number of pathogens, including bacteria, viruses, and parasites. Bacterial-induced pneumonia is the primary cause of respiratory infections worldwide. The primary bacterial pathogen associated with pneumonia is S. pneumoniae, although other agents such as Mycoplasma pneumoniae are frequently found. Over 500,000 cases are estimated to occur annually in the U.S. Between 25,000-50,000 deaths/year are associated with this disease. Pneumonia and influenza together constitute the fourth leading cause of death among the elderly. Two other viruses associated with serious respiratory infection in infants and children are Respiratory Syncytial (RS) Virus and Parainfluenza (PI) virus. It is estimated that 24 percent of the cases of pneumonia are the direct result of RS or PI virus infections. The mortality rate is high. The frequency and severity of this disease makes research in the prevention and therapy of pneumonia a top priority.

In conjunction with USAID, a clinical study has been initiated in The Gambia to evaluate the serotype distribution of pneumococcal antigens and the prevalence of pneumococcal disease in this geographic location with regard to mortality and morbidity in infants and children. This information will give information on the extent of this disease and the specific organism(s) responsible which, in turn, will be important for the development of new vaccines and for the conduct of future clinical trials to evaluate the efficacy of candidate pneumococcal vaccines.

Amantadine HCl, an antiviral compound currently approved in the U.S. for the prophylaxis and treatment of influenza A infections, has not been extensively used due, in part, to the associated side effects. Rimantadine does not appear to have the side effects associate with amantadine and thus may be more widely used in high risk populations, such as the elderly. An application for licensing of rimantadine for the prophylaxis and treatment of influenza A virus infection, a major cause of pneumonia in the elderly, was reviewed and endorsed by the FDA Advisory Panel in 1987.

There is currently only one antiviral agent, ribavirin, licensed for use in RS Virus infections. Through NIAID's _in vitro_ screening facilities, three additional compounds have been identified with selective activity against RS and PI viruses. These compounds are currently undergoing further evaluation and one has advanced to animal model testing.

Influenza

Influenza has long been recognized as a major uncontrolled health problem in the U.S. In the U.S., approximately 20-25 percent of the population suffers from influenza each year. These influenza epidemics are associated with significant mortality since influenza and pneumonia still rank as the fifth or sixth leading cause of death in the U.S. Vaccination continues to be the focus of control, but only about 25 percent of the recommended groups are vaccinated. Thus, in addition to basic research efforts on the understanding of the pathogenesis and variation of this virus, much effort has been devoted to the development of alternative prophylactic and therapeutic approaches for the control of influenza virus infections.

A synthetic molecule capable of disrupting replication of influenza virus has been evaluated in the mouse model. The identification of a targeted molecule capable of interfering with the replication of all major influenza virus types is unique and encouraging.

The cold-adapted (_ca_) live influenza virus vaccine has been evaluated in over 17,000 people. The safety and efficacy of this vaccine approach has been demonstrated. Limited evaluation of the comparable efficacy between the _ca_ vaccine and the inactivated vaccine has suggested that a greater efficacy can be attained in children when the ca vaccine is used. Both the ca and inactivated vaccines appear to be equally effective, but the administration of the ca vaccine using nose drops will make it easier to use and offers the opportunity to dampen the impact of influenza epidemics by actively immunizing children and preventing or limiting the spread of influenza in schools.

An application for licensing of rimantadine for the prophylaxis and treatment of influenza A virus infection, a major cause of pneumonia in the elderly, was reviewed and endorsed by the FDA Advisory Panel.

Antivirals, Immunology and Infectious Diseases excluding AIDS

Viral infections cause significant morbidity and mortality in the United States and the rest of the world. Since viruses replicate inside cells and subvert cellular functions for their own use, the identification of compounds which selectively inhibit viral replication without irreparably harming the host is much more difficult than isolating agents active against free-living bacteria. Two approaches are used. The first is to identify agents with possible therapeutic activity by in vitro screening of available chemicals and natural products and by the chemical synthesis of novel structures. The second approach is to take advantage of recent advances in the understanding of the molecular events of viral replication and to use this information to synthesize compounds that specifically inhibit viral replication steps and do not affect cellular biochemistry. Candidate compounds must be evaluated in animal models before they can be entered into clinical evaluation.

A recently completed clinical trial demonstrated that acyclovir was equally as efficacious as vidarabine for the treatment of neonatal herpes simplex infections. This finding will significantly improve therapy since acyclovir is easily administered.

NIAID investigators demonstrated that HPMPC, a compound being developed by Bristol-Myers Co., is more effective therapeutically than ganciclovir in a mouse model of cytomegalovirus infection.

A possible primate animal model for human genital papillomavirus infections has undergone preliminary characterization. The natural history of this primate disease may be analogous to human disease in that this infection is usually silent, it may be sexually transmitted, and it may be associated with eventual development of a squamous cell carcinoma.

Sixty compounds have been evaluated by NIAID's antiviral screening facilities to date. Several compounds have been identified with selective activity against herpes viruses, respiratory syncytial virus, influenza or parainfluenza. Further in vitro evaluation of each is underway and several have advanced to animal model testing.

Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS) is a multisystem syndrome characterized by months of debilitating fatigue frequently associated with recurrent sore throat, low grade fever, myalgia, headache, gastrointestinal symptoms and tender lymph nodes. The public health importance of CFS cannot be fully assessed without data on the prevalence of the syndrome and knowledge of its natural history. Therapies cannot be evaluated without clinical or laboratory markers of disease remission and without appropriate controls. Determination of cause and mechanisms of pathogenesis require clinical and epidemiologic studies that incorporate well-defined cases and controls.

Two important epidemiologic studies have been initiated: one to estimate prevalence of CFS in a population-based HMO and the other in a general medical practice.

Test results indicate that patients in a NIAID intramural study have reduced adrenal function and neuroendocrine patterns that are distinct from persons suffering from depression. This is an important finding which may identify a constitutional susceptibility factor.

Sexually Transmitted Diseases (STDs)

During the last half of this century there have been dramatic increases in sexually transmitted diseases (STD's) in the United States:

Gonorrhea - Annually, approximately 2 million new cases at an estimated cost of almost $1 billion; 25 percent of the cases are in teenagers; four new types of antibiotic resistance have emerged in the last decade.

Chlamydial Infection - Annual incidence of approximately 4 million cases at a comprehensive cost in excess of $1.4 billion; control is complicated by the frequency of asymptomatic disease, the cost and technical difficulty of available diagnostic tests, and the absence of effective single dose therapy.

Syphilis - In 1987, the largest single-year increase in infectious syphilis in more than a quarter of a century was reported; the increase in women was followed by a 21 percent increase in the rate of congenital cases.

Chancroid - Since 1980, the annual incidence has increased more than 500 percent due to multiple outbreaks across the country.

Genital Herpes (HSV) - Approximately 30 million Americans are afflicted with this painful, recurrent, incurable disease.

Human Papillomavirus (HPV) Infection - Approximately 24 million people are infected with this virus, which remains extremely difficult to detect and eradicate.

STDs have long-term, devastating consequences, which disproportionately affect women and infants:

Pelvic Inflammatory Disease (PID) - Untreated or inadequately treated gonococcal and chlamydial infections result in approximately 1 million cases of PID each year. By FY 1990, estimated PID health care costs will total $3.5 billion. Consequences include scarring of fallopian tubes leading to infertility, life-threatening tubal pregnancy, and chronic pelvic pain syndromes.

Adverse Outcomes of Pregnancy - STDs are preventable causes of fetal wastage, low birth weight, and congenital infection in one quarter to two thirds of acutely infected women.

Cervical Cancer - Infection with several biotypes of HPV are associated with the development of cervical carcinoma.

HIV Transmission - In both men and women, STDs, particularly those infections that result in genital ulcers, such as syphilis, herpes, and chancroid, markedly increase the risk of HIV transmission.

Recent accomplishments by NIAID sponsored research includes the following:

Gonorrhea - Recent efforts have identified conserved surface-exposed sites on stable outer membrane proteins. Monoclonal antibodies directed toward these sites facilitate killing of bacteria. Studies of other surface proteins have revealed either antigenic variability or dominant "blocking" sites, diminishing enthusiasm for these antigens as vaccine candidates.

Chlamydial Infection - Establishment of an endometrial tissue culture system has added to understanding of attachment and entry into host cells. Development of mouse and guinea pig models have provided insights into molecular mechanisms of tubal infection and scarring.

Syphilis - A major impediment to understanding this disease has been the inability to culture the causative organism, T. pallidum. Through recombinant technology many T. pallidum proteins are now synthesized in E. coli, making them easy to isolate and analyze. Molecular immunology and studies on molecules which mediate adherence to host cells are examining the pathogenesis of syphilis.

HSV - Several Phase I vaccine trials are beginning using a variety of viral proteins, some from recombinant systems. Roles of gamma and alpha interferon in ulcer regression are under investigation. A gene has been identified which appears to be essential for reactivation of lesions, although it is not necessary for latency.

HPV - Extremely sensitive methods for detection of viral DNA such as polymerase chain reaction (PCR) have been developed. Also in progress are studies analyzing cofactors involved in viral replication, which may elucidate HPV's role in cervical carcinoma. Growth of the virus in a mouse renal-tissue graft is a major advance. Two program project grants, focusing on the natural history of HPV infection have been awarded.

PID - Studies on molecular mechanisms of damage to the fallopian tube have revealed that a tissue factor, tumor necrosis factor (TNF), may mediate these events. TNF effects can be blocked by prostaglandin inhibitors. The roles of risk factors such as douching and oral contraception in development of PID are being elucidated. Efficacy of intervention strategies such as screening tests and partner-notification are being evaluated.

AIDS Research Program

NIAID AIDS Program

The Division of the Acquired Immunodeficiency Syndrome (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID) was created in 1986 to address national research needs created by the advent and spread of the acquired immunodeficiency syndrome (AIDS) epidemic. Integral to the Division's mission is responsibility for ensuring that scientific investigation of infection with the human immunodeficiency virus (HIV) is focused on the most critical biomedical research issues engendered by the AIDS epidemic.

The NIAID key research goals are: to decrease or prevent the spread of infection by HIV, to curb disease progression in people who are infected by the virus but do not have symptoms, and to limit disease progression and mortality in people with AIDS while preserving a high quality of life. Working toward these ends, NIAID supports preclinical and clinical research directly geared toward developing new treatments and potential vaccines for AIDS. These research activities also include the basic science foundation needed to advance drug and vaccine development, including studies in epidemiology, HIV pathogenesis, and biostatistics research.

Treatment research supported by NIAID is built around a large network of multi-center clinical trials, which evaluate potential AIDS therapies. These critical studies are assessing the safety and efficacy of new drugs and drug combinations in patients at various stages of HIV infection. This enormous effort reaches HIV-infected people in all affected population groups in many major metropolitan areas around the U.S. Another facet of clinical trials research is a new community-based research program, which is expanding the arena of AIDS clinical research to include such settings as community-based clinics. This endeavor taps the expertise of community physicians in treatment research and broadens patient access to the clinical drug development process.

Feeding drugs into the clinical trials system is a large effort in pre-clinical drug development. These studies use various animal models of retroviral infection to test potential new drugs for AIDS and its associated diseases, the opportunistic infections and malignancies that are a significant cause of sickness and death in AIDS patients. Through a highly-organized, collaborative structure, researchers are examining potential new agents and drug combinations for safety and efficacy. New drugs are currently entering the clinical trials system as a result of this work.

The development of a vaccine for HIV infection is a key goal of NIAID-supported research. Basic research studies are expanding knowledge of the mechanisms of immunity to HIV as well as information on the most promising candidate vaccines. A substantial, collaborative structure supports animal studies that are examining the effects of a wide range of potential vaccines in several retroviral models. As a result of this important work, clinical trials of candidate vaccines have recently begun.

Research that underpins all the activity in drug and vaccine development includes a range of research projects that are providing critical information for the more applied research areas. The fields of epidemiology, pathogenesis, and biostatistics research are building a knowledge base about HIV infection and associated diseases that is critical to treatment and vaccine development. NIAID-sponsored epidemiologic studies strive to identify the mechanisms of HIV transmission, characterize and provide data on the natural history of HIV infection and related diseases, and develop the knowledge base for interventions for high-risk populations and general treatment of HIV-infected patients. Several large, multi-center epidemiologic research projects are underway. These important studies are revealing the course of the disease in various populations and critical information on HIV transmission.

Another area that strives to build a foundation of knowledge for the applied research areas is research of the pathogenesis of HIV infection. Studies in HIV pathogenesis aim to increase understanding of the biology of HIV by multi-disciplinary study of such aspects of the virus as its life cycle and its effects on the host. Knowledge gained from these studies enhances the ability of researchers to create new agents and vaccines to combat HIV infection. The Centers for AIDS Research endeavor provides core resources and enhances collaboration in AIDS-related basic research.

NIAID-supported and -conducted biostatistics research ensures the use of appropriate statistical methodology in the design and analysis of clinical, epidemiologic, and laboratory studies. This work is developing optimal approaches to the statistical issues concerning AIDS research.

Coordinating this panoply of AIDS research activities is an important function of NIAID. By surveying developments in key program areas, the Division assesses ongoing needs in biomedical research as well as requirements for outreach activities and for training scientific investigators. As part of this process, the Division works with advisory groups and voluntary and health professional organizations, evaluating and redirecting program emphases to accommodate changing research needs.

The Division fosters broadly based collaboration in specific programmatic areas. A consortium of organizations called the AIDS Clinical Trials Group (ACTG) brings together clinical investigators and their institutions, the ACTG Statistical Data and Analysis Center, the Food and Drug Administration (FDA), the pharmaceutical industry, patients with HIV infection and their advocates, and appropriate NIAID staff to make key decisions about AIDS treatment research issues. In the basic sciences, two cooperative groups create a link between researchers in government, industry, and academia to promote the rapid discovery and development of new potential treatments and vaccines. The National Cooperative Drug Discovery Groups foster coordination, collaboration, and information exchange among these groups in the area of drug discovery. The National Cooperative Vaccine Development Groups perform similar functions for vaccine research.

The Division of AIDS sponsors research through research project grants (both unsolicited and solicited), research centers, contracts, and cooperative agreements. Several major contracts provide critical resources to the Division and to researchers nationally. These contracts include the Statistical Data and Analysis Center, which analyzes incoming data from AIDS clinical trials; the AIDS Research and Reference Reagent Program, which makes research reagents available to basic researchers; and the National AIDS Clinical Trials Information Service, which advises telephone callers on the status of AIDS clinical trials.

Recent Accomplishments

AIDS Drug Development

Optimism exists for the discovery and development of improved therapies for treating AIDS and preventing the spread of HIV infection. New therapies, including ddI, are now undergoing clinical trial to evaluate their safety and anti-HIV potential, and at least two drugs have been approved for the treatment of opportunistic diseases.

National Cooperative Drug Discovery Group (NCDDG) investigators established a simple, rapid assay to screen a large number of synthetic compounds and natural products for their ability to inhibit HIV tat function. The group has examined approximately 7,000 compounds to date and identified a lead compound with anti-tat activity.

An NCDDG group reported that certain synthetic peptides strongly inhibit the HIV protease. More importantly, the peptides, now in preclinical development, inhibited HIV replication in cultured cells.

Another NCDDG team identified synthetic peptides (including transition state analogs) that inhibit HIV protease and viral replication in cultured cells. In collaboration with NCI investigators, they determined the crystal structure of the protease-inhibitor complex to facilitate the design of more selective and potent inhibitors.

A combination of two clinically available drugs, clindamycin and primaquine was identified by a contractor as exhibiting excellent activity against *Pneumocystis carinii* both *in vitro* and in an animal disease model. This combination is undergoing clinical evaluation.

Preliminary data indicate that HIV infection of human cells in the SCID/hu mouse can be partially prevented or slowed by treatment with zidovudine. These findings also demonstrate that SCID/hu mice may be a valuable model for testing potential new drugs.

Discovery by a contractor that SIV can be transmitted across the lining of the genital tract into the blood stream constitutes the first time that infection with a virus similar to HIV has been successfully established by any means of transmission other than direct injection into the blood.

Several models have been developed to investigate the activity of drugs on the transmission of a murine retrovirus from mother to progeny. Studies have found that both virus and drugs such as zidovudine are present in the milk of nursing mothers. Newborn mice were at least partially protected from infection and/or disease by early treatment with zidovudine.

Based on the finding that *P. carinii* may be a fungus rather than a protozoan, contractors have developed a synthetic growth medium which will support the growth of *P. carinii* in the absence of other cells. This accomplishment will contribute to the study of the organism's metabolism and sensitivity to antimicrobials.

AIDS Clinical Trial Groups

The testing of drugs as potential treatments for HIV infection and its sequelae is a key imperative of HIV research. NIAID sponsored scientists through the AIDS Clinical Trial Groups (ACTG's) have accomplished the following:

1. Antiretroviral Therapy

ACTG-supported research produced two landmark advances in the treatment of HIV infection this year. Protocol 019 furnished the first evidence that zidovudine can delay disease progression in HIV-infected asymptomatic people with CD4+ counts of less than 500. Another advance in AIDS treatment research this year emanated from protocol 016, which showed that participants with early AIDS Related Complex (ARC) progressed to advanced ARC or AIDS significantly more slowly on zidovudine therapy than placebo.

NIAID has begun analysis of the data from protocol 002, comparing the benefits of high and low doses of zidovudine. The data reveal that low doses of zidovudine are at least as effective in prolonging life in AIDS patients as the standard dose and are less toxic.

Another recent study showed that the drug probenecid can effectively reduce the body's degradation of zidovudine which increases its affect.

This year, four new antiretrovirals entered phase I clinical trials: ddI, N-butyl DNJ, soluble CD4, and d4T. A phase I trial of ddI in patients with AIDS or ARC showed the drug to be extremely well-tolerated with some preliminary evidence of efficacy. Also completed this year was a phase I/II trial of ddC; further studies are comparing alternating regimens of zidovudine and ddC. A phase I trial is ongoing of soluble CD4 in patients with AIDS or advanced ARC and it appears that the CD4 is well tolerated.

2. Opportunistic Infections

Aerosolized pentamidine was recently awarded treatment investigational new drug (IND) status as a prophylactic therapy for Pneumocystis carinii pneumonia (PCP). Further research is now aimed at identifying the best prophylaxis for PCP infection. Protocol 021 is evaluating the effectiveness of aerosolized pentamidine and trimethoprim-sulfamethoxazole to prevent the recurrence of PCP. Protocol 081, is comparing three treatments: aerosolized pentamidine, trimethoprim-sulfamethoxyazole, and dapsone in patients who have never had PCP, but have low CD4+ counts.

Several clinical trials are examining potential therapies for PCP. For mild to moderate PCP, the ACTG is assessing the safety and efficacy of clindamycin and primaquine (protocol 044) in patients with AIDS. A protocol under development (108) will compare the value of clindamycin plus primaquine versus dapsone plus trimethoprim.

Together with the drug company Pfizer, the ACTG conducted a study of fluconazole for treating cryptococcyl meningitis. This drug appeared to be better tolerated than amphotericin, the standard therapy.

The recent Food and Drug Administration (FDA) approval of ganciclovir for cytomegalovirus retinitis was a major achievement in AIDS therapeutics this year. This progress resulted from a study that provided safety information leading to a treatment IND and ultimately full FDA approval.

Also completed this year was a phase I trial (protocol 015) of foscarnet. This trial led to two new studies: a study of foscarnet as a salvage therapy and another comparing the efficacy of ganciclovir and foscarnet. Preliminary results of foscarnet are promising.

3. Pediatrics

From October 1988 to November 1989, 680 cases of AIDS were reported among children under 13 years of age compared to 575 during the previous 12-month period. Since June 1981, over 1,900 children have been reported with AIDS. Seventy-nine percent of children who were reported to have AIDS in the past 12 months (since October 1988) are black or Hispanic. A new trend is that more children are now being born to mothers who acquired HIV heterosexually rather than through intravenous drug use. The numbers of ill and dying children are expected to increase over the next decade. The NIAID funds 15 ACTU sites for conducting studies confined to pediatric patients, and seven additional centers which study adults are now including evaluation of drug treatment of HIV infection in children.

Recent ACTG studies contributed to the FDA award of treatment IND status to zidovudine for children three months to 12 years of age who have AIDS or symptomatic HIV infection. This advance will make zidovudine the first treatment for HIV infection to become widely available for children. Further, these studies found that side effects were similar in adults and children.

Another key pediatric clinical trial (protocol 051) is studying the therapeutic potential of intravenous gamma globulin plus zidovudine for children with AIDS or ARC. Protocol 128, about to begin, is comparing two doses of zidovudine in mildly symptomatic three months to 12 years of age.

A key scientific thrust in pediatrics is the attempt to treat HIV infection earlier in the course of the disease or to block its transmission. Several studies are underway using zidovudine in both newborns and pregnant women. Protocol 049, a phase I study in infants exposed to HIV at or before birth, has almost finished accruing patients. Key data from this trial will allow the development of a phase III trial (protocol 076) in newborns.

ACTG has initiated its first clinical trial of zidovudine in pregnant women (protocol 082). The phase I study will look at ten HIV-infected women given zidovudine in the last trimester of pregnancy and at delivery. These studies will monitor the effects of zidovudine on pregnancy and on neonates and will help determine whether zidovudine can be safely given to intravenous drug users (IVDU's) or women on methadone maintenance.

Batch testing of p24 HIV viral antigen has been completed for multiple protocols permitting the evaluation of the therapeutic effects on viral parameters in these studies.

AIDS Vaccine Development

The support of research aimed at expediting the development and testing of AIDS vaccines is a high priority. For AIDS vaccines, development of adjuvant technology has also become an important focus in efforts to potentiate immune responses to candidate vaccines.

Perhaps the most dramatic advance in AIDS vaccine development thus far is the recent evidence from several animal studies that experimental lentiviral vaccines, using novel adjuvants, can protect against the establishment of infection and AIDS-like disease. These studies demonstrate the scientific feasibility of AIDS vaccine development and could potentially have an impact on the timetable for success.

The first FDA-approved Phase I clinical trial of a research AIDS vaccine is currently being evaluated in our intramural program. Intramural NIAID scientists played a major role in the preclinical development of this experimental vaccine.

The NIAID Vaccine Evaluation Units, a network of six contractors serving as a national resource for the evaluation of vaccines, are presently conducting Phase I testing of two experimental AIDS vaccines.

The genetic variation of HIV continues to be a major hurdle in vaccine development. NIAID has expanded the efforts of the HIV genetic sequence database by funding contracts (HIV Genetic Variation Program) to clone and sequence strains of HIV from different geographical locales and from different time points in infected individuals to obtain a better understanding of the magnitude of genetic variation and its impact on vaccine development.

Research was expanded into the development of vaccine adjuvants. An AIDS Cooperative Adjuvant Group has been established to facilitate the interaction of researchers studying vaccine adjuvants with those studying AIDS vaccines and to facilitate the necessary comparative studies to replace alum, which is currently being used, with a safe but more efficient adjuvant.

Minorities

Epidemiologic studies show that over 43 percent of AIDS cases in the U.S. occur in non-whites. Minority patients with HIV infection represent a special population with unique social, economic, and medical problems. Further, a wealth of information can be obtained from study of populations other than those studied in detail to date, i.e., middle class, white, homosexual men. Data indicate that there will be a continuing large increase in the numbers of symptomatic and dying children over the next decade. The majority are black or Hispanic. There is a pressing need for perinatal transmission studies, early identification of infection in newborns, effective treatment for infected children, and methods to prevent perinatal HIV transmission. Infected women are disproportionately of minority background, and their prevention and treatment needs deserve special consideration, given the lack of available information on differences between men and women. An estimated 90 percent of funds for the Women and Infants Transmission Study and 93 percent of funds for the Heterosexual HIV Transmission Study are devoted to underrepresented populations. Minority patients and minority investigators are proportionately underrepresented in the efforts directed at the development of therapeutics for HIV infection.

The Multicenter AIDS Cohort Study (MACS) has specifically developed protocols to recruit additional non-white homosexual men for prospective longitudinal studies by expanding outreach to homosexual minority communities and their leaders. Currently, minorities account for approximately 13.8 percent of the total MACS cohort.

The NIAID grant portfolio of investigator-initiated epidemiologic research studies includes: a natural history study of HIV infection in Haitians (both in Haiti and Miami); a perinatal transmission study in Haiti; a study to evaluate correlations between STDs and HIV infection in black men in Los Angeles; and a heterosexual transmission study in Zaire.

NIAID has awarded grants to U.S.-based institutions to establish five to seven ICARS. The majority of participating countries have predominantly black or Hispanic populations.

Eleven international grants are studying natural history and transmission especially among persons who are ethnic minorities in the United States.

NIAID is encouraging investigators at the 47 institutions comprising the ACTG network to make greater efforts to increase the representation of people from minority groups in ACTG studies as well as in other avenues of clinical research.

The two issues in Intra-Venous Drug User (IVDU) participation in ACTG studies are impediments to study entry and compliance following enrollment. A recent analysis of patients evaluated at the University of Massachusetts for enrollment into ACTG studies found that significantly fewer of the 141 IVDUs were enrolled compared to the 78 non-IVDUs (7.8 percent vs. 24.4 percent). Additionally, only one-third of the IVDUs were deemed eligible compared to about one-half of the non-IVDUs.

International AIDS Activities

The rapid spread of HIV infection has made AIDS a worldwide public health problem. Although the pathogenesis of HIV infection appears to be similar in various affected geographic regions, differences in epidemiology, clinical presentation of disease, and other factors suggest that programs for the prevention and control of AIDS should include maximal international collaboration. A thorough understanding of the epidemiology of the HIV infection in areas of high disease incidence will be essential to the design of successful vaccine trials. Through its International Collaborative AIDS Research (ICAR) awards, NIAID supports clinical epidemiology studies following cohorts of individuals at high risk for HIV infection in several international sites.

NIAID continues to support and maintain an active role in Project SIDA, a multi-disciplinary program in clinical epidemiology, virology, and immunology located in Kinshasa, Zaire.

Epidemiologic studies of HIV infection in the Caribbean and Latin America are being initiated under a research contract with the Pan American Health Organization.

Projects have recruited several thousand pregnant women into prospective cohort studies for the study of perinatal transmission and have documented seroprevalence rates among selected populations in Uganda, Mexico, Brazil, Zaire, and Malawi.

Of over 2,000 pregnant women tested in Uganda, over 25 percent were found to be HIV positive. Over 150 people with TB or KS and HIV infection are being followed to study opportunistic infections associated with HIV infection.

In Malawi, ICAR researchers have detected increased fetal wastage associated with HIV infection and have studied the use of medicinal preparations as a possible co-factor increasing susceptibility to infection among women.

In Brazil, researchers are documenting changes in seroprevalence levels in special populations. For example, in blood bank blood they found seroprevalence rates of 0.20 - 0.77 percent in the most recent periods. A study of hemophiliacs detected increased levels of beta-2-microglobulin prior to seroconversion. Seroprevalence in prisons rose from 3 to 15 percent in one year in one prison and from 15 to 20 percent in another prison in a year. Studies of prostitutes have detected prevalence levels of 0 to 17 percent in different areas.

Collaborative Projects

The PHS Executive AIDS Task Force and virtually all of its various subcommittees have NIAID representation. Preclinical drug development is closely coordinated with the NCI, which has the primary responsibility for drug screening, while the NIAID has the lead on targeted drug development and clinical trials of new agents for both HIV infection and the opportunistic infections associated with it.

The National Hemophilia Foundation (NHF) has established a national network of treatment centers for hemophilia. In collaboration with the NHF, the NIAID is using this network to conduct a major clinical trial of AZT in asymptomatic hemophiliacs.

The NIAID is also collaborating with the National Institute of Child Health and Human Development in the design and implementation of the largest and most comprehensive study of Vertical Transmission of HIV. Both Institutes contribute both technical and financial resources to this important study.

The NIAID is collaborating with the Department of Defense in a second study of perinatal transmission of HIV infection located in Newark, New Jersey.

NIAID has contracted with the Pan American Health Organization to design and implement studies of the epidemiology of HIV infection in various countries in South America and the Caribbean.

A long-term multi-center prospective cohort study of the pulmonary complications of HIV infection has been developed and initiated in collaboration with the NHLBI.

A major effort of the NIAID is directed toward sequencing of the HIV and SIV genomes. The Centers for Disease Control (CDC) is a major collaborator in this effort, performing much of the gene sequencing work on various HIV and SIV isolates. The Department of Energy (DOE) is another pivotal collaborator in this effort. The HIV Sequence Database and Analysis Unit of the Project is located at DOE's Los Alamos Laboratories.

The NIAID and the National Eye Institute have worked closely together and with the FDA and two separate pharmaceutical companies in developing studies of new agents for the treatment of Cytomegalovirus retinitis.

The NIAID, the FDA, the National Library of Medicine (NLM), and the CDC have jointly developed a database of information on HIV clinical trials. The National AIDS Clinical Trials Information Service (NACTIS) provides telephone-based information to public callers. The NLM is making this database available to the public through their international computer resource.

Future Research Plans

Drug Development

The NIAID has established long-range plans to address all aspects of drug discovery and development. The following activities are planned for FY 1991:

Many top research groups are working within the NCDDG program on targeting therapies to each of the major steps of viral replication. The ongoing success of this program requires continued support of top scientists from diverse fields working together with the facilitating activities of DAIDS.

Clearly, there is a need to intensify research efforts toward understanding and controlling deadly and debilitating OIs. Modeled after the highly successful NCDDG-AIDS program, the National Cooperative Drug Discovery Group Program for the Treatment of Opportunistic Infections Associated with AIDS (NCDDG-OI) was launched in FY 1990 to support research on OIs. Further expansion of this effort is planned and will enable the study of a myriad of OIs seen in AIDS patients.

The Institute plans to make available supplemental funds to enhance its efforts in the area of pediatric HIV infection. Applications will be sought from existing ACTUs, whether or not they have previously been involved in pediatric studies. In addition to providing the highest scientific standards in conducting these trials, applicants will also be expected to address the social, legal, and economic issues facing patients who may be economically deprived, non-English speaking, or otherwise disadvantaged.

The rate of progression to ARC and AIDS is increasing in the hemophiliac population. Therefore, new initiatives are planned to address this serious but inevitable occurrence. Also, in response to requests from the hemophiliac community, we are currently developing a mechanism by which the coordination centers and the Hemophilia Treatment Centers can participate in a wide range of protocols with the ACTG.

AIDS Clinical Trial Groups (ACTGs)

The science of AIDS clinical research has evolved to the point at which researchers can, for the first time, compare the benefit of several drugs to determine the optimal treatments for several of the opportunistic infections affecting AIDS patients. These comparative clinical trials will become an increasingly important thrust in research of drugs for opportunistic infections as well as primary HIV infection.

The expansion of the pediatric ACTUs in 1988 enabled researchers to begin phase II and phase III pediatric clinical trials. NIAID will expand the ACTG with special emphasis on the participation of minorities, intravenous drug users, and women.

NIAID will sponsor a consensus conference to assure optimal technology transfer from protocols 016 and 019. The conference will establish recommendations for the use of zidovudine therapy in routine medical practice for patients with early HIV infection.

AIDS Vaccine Development

Expand the National Cooperative Vaccine Development Groups and establish a project for AIDS vaccine development consisting of research and development, clinical trials, and an expanded information/surveillance network serving to link all investigators working on AIDS vaccine development to facilitate information and reagent exchange.

Establish a Centralized Core Immunology Laboratory to facilitate testing of humoral and cell-mediated immune responses and monitor quality control of candidate AIDS vaccines being tested in the AIDS Vaccine Evaluation Units.

Expand efforts in primate model development for AIDS with emphasis on the SIV model as well as efforts in vaccine adjuvant development.

Begin the process of developing the capacity to undertake Phase III efficacy trials of AIDS vaccines. It is anticipated that Phase III efficacy trials will require large numbers of volunteers at high risk for HIV infection, and may entail two or more years of follow-up for evaluation of vaccine efficacy.

Increase support of basic research particularly in immunological areas of T-lymphocyte activation and novel vector construction and provide reagents and research resources to test experimental AIDS vaccines in appropriate animal models.

Minorities

Continue collaboration with the Pan American Health Organization to study AIDS in four Latin American and Caribbean countries where the populations are largely Hispanic.

Continue support of current epidemiologic research contracts and grants.

Continue development of data center mechanisms to collect and integrate data and findings from the HATS and WITS studies.

Continue efforts to increase the enrollment of minority homosexual and bisexual men within the MACS.

International AIDS Activities

NIAID will be expanding its support to maintain the requisite laboratory and clinical expertise at national and international locales where potential AIDS vaccines may be evaluated in Phase III trials.

NIAID will continue to work closely with the World Health Organization and other international agencies involved in the clinical evaluation of AIDS vaccines.

Community Programs for Clinical Research on AIDS

An RFP will be issued in early FY 1991 with hopes of expanding the CPCRA initiatives. The institute plans to increase the number of awards in FY 1991.

Phase III AIDS Clinical Trials

NIAID will be expanding its support to develop and maintain the requisite laboratory and clinical expertise at national and international locales where potential AIDS vaccines may be evaluated in Phase III trials.

NIAID will continue to work closely with the World Health Organization and other international agencies involved in the clinical evaluation of AIDS vaccines.

National Institute of Allergy and Infectious Diseases

Allergy, Immunology and Transplantation

1991 Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$160,254,000	$167,260,000	+$7,006,000

Purpose and Method of Operation

The Allergy, Immunology and Transplantation activities focuses on the immune system as it functions in the maintenance of health and as it malfunctions in the production of disease. It encompasses both basic and clinical research.

Basic research is conducted under two segments: immunobiology and immunochemistry, and immunogenetics and transplantation immunology. Clinical research is supported in two areas: asthma and allergic diseases, and immunological diseases and immunopathology. NIAID's approach integrates the basic science disciplines with relevant clinical specialties.

The NIAID focuses upon initiatives by fostering individual investigator initiated research and providing support for multi-disciplinary program projects dealing with the mechanisms of immunologic diseases, transplantation immunology and the basic biology of the immune system. In addition, the NIAID provides support for interdisciplinary research centers on asthma and allergic diseases and immunologic diseases.

The cause, pathogenesis, diagnosis, prevention, and treatments of allergic diseases are of NIAID concern. Various types of allergic problems are currently under investigation such as: immediate type hypersensitivity and its disorders, including asthma, allergic rhinitis, atopic dermatitis, and allergic reactions and disorders caused by insect bites and stings, foods, airborne allergens, and infectious agents; manifestations of delayed hypersensitivity and contact dermatitis; and the mechanisms of drug reactions and chemical sensitization.

NIAID promotes the interaction of basic and clinical scientists by supporting specialized Asthma and Allergic Disease Centers which conduct research on the causes, prevention, and treatment of these disorders. Centers encourage collaborative studies among immunologists, geneticists, biochemists, pharmacologists and clinicians.

NIAID supports studies in basic immunology concerned with the properties, interactions and functions of the cells of the immune system and the products elaborated by those cells. Recognizing that the information gleaned from fundamental, untargeted research is the raw material from which clinical stratagems and biotechnical applications are fashioned, the NIAID supports a broad range of research concerned with basic structure and function of the immune system, including: the origin, maturation and interactions of lymphocytes, antigen-presenting cells, and effector cells; identification and characterization of the antigen-specific receptors of lymphocytes; the cellular and molecular events involved in the initiation, maintenance, regulation and termination of immune responses; characterization of cytokines and their receptors; the regulation of immunoglobulin and lymphokine synthesis and secretion; and the description of the biochemical and macromolecular events in lymphocyte activation. In addition, the NIAID supports Program Projects on the Biology of the Immune System, which focus upon the biologic and chemical structure of the immune system to help understand the basic cellular and molecular immune responses in health and disease.

Rationale for the Budget Request

The FY 1991 budget estimate of $167,260,000 for allergy, immunology and transplantation represents an increase of $7,006,000 or four percent over the FY 1990 estimate. The following are new initiatives NIAID will undertake in FY 1991 under the allergy, immunology, and transplantation program:

Immune System and Its Disorders

Encourage and support expanded research on the properties, characteristics and functions of the human immune system through the use of recently-developed model systems and the development of improved model systems and encourage immediate utilization of this model system to study human allergic immune reactions.

Support expanded research efforts concerned with elucidating the structure and function of key immunological processes that involve T cell receptors, cell-adhesion molecules, interleukins and their receptors in both human systems and laboratory animal models. Promote the rapid progress on the preparation and utilization of therapeutic human T cell clones for the treatment of selected human autoimmune disorders, e.g., multiple sclerosis and celiac disease.

Foster progress in elucidating the structural and functional features of the mucosal immune system. Initiate efforts to gain a better understanding of orally-induced immunological tolerance, the selective migration and localization of mucosal antibody-producing cells, and the unique action of cholera toxin as an adjuvant for enhancing mucosal immunity in important sites such as the upper respiratory tract. Facilitate the rapid development of clinical trials on the use of cholera toxin-antigen conjugates for inducing effective local immunity in humans.

Immune System and Environment Immunotoxicology

Promote the development and expansion of the basic research base by encouraging collaboration between and among pharmacologists, toxicologists, immunologists and others.

Encourage the development of newly devised/defined approaches to the study of environmentally-induced disorders where putative immunologic mechanisms are thought to be responsible.

Encourage and/or establish pre- and post-doctoral training programs designed to incorporate the disciplines relevant to the newly emerging science of Immunotoxicology.

Allergy

Pursue basic research concerning histamine releasing factors and their naturally occurring inhibitors.

Pursue sampling experiments of nasal washing, blister fluids, and lung fluids for characterization of cells and mediators responsible for allergic inflammation.

Determine the role of IgE+ in late phase allergic responses.

Characterize the role of cytokines on the functions of cells associated with allergic and inflammatory diseases.

Asthma

NIAID plans to design and evaluate a comprehensive, two-phase intervention program to reduce asthma-related morbidity for African American and Hispanic children residing in the inner city. The objective of the first phase is to elucidate those factors that contribute to asthma morbidity for children in the targeted population. Using the information gained from phase one, phase two will serve to develop, implement, and evaluate a feasible clinical intervention program to achieve long-term reduction in asthma morbidity for the children residing in the inner city.

Develop therapeutic strategies to diminish early and late phase allergic responses.

Pursue the role of early exposures to viruses and allergens, by both oral and inhaled routes, and the development of asthma.

Determine factors leading to increased hospitalizations and mortality from asthma.

Design interventions to reduce hospitalizations and mortality from asthma.

Genetics and Autoimmune Diseases

The NIAID will initiate program project grants on autoimmune mechanisms of disease in order to develop integrated studies involving both basic science research and clinical investigation aimed at elucidating the etiology and pathogenetic mechanisms involved. Improve the diagnosis, treatment, and prevention of a wide variety of autoimmune disorders.

The cloning and sequencing of additional disease-related HLA genes will be encouraged in order to support the development of new diagnostic and screening procedures and the design of new therapeutic strategies for the prevention of autoimmune disease in susceptible individuals.

We plan to support basic studies concerning the genetic and immune mechanisms responsible for the induction and pathogenesis of autoimmune diseases. The information provided by these studies should enhance the development of new and improved drugs for the treatment of immunologic diseases.

Genetics and Transplantation Biology and Organ Transplantation

We will continue the support of two clinical trials where the effectiveness of new monoclonal anti-T lymphocyte antibodies will be studied in kidney transplant patients. The goal of these important studies is to develop new reagents and regimens to prevent graft rejection and minimize the harmful side-effects associated with current immunosuppressive therapies.

We plan to support a Cooperative Clinical Trial in Transplantation. This network of kidney transplant units would conduct a series of multi-center clinical trials to evaluate new and currently used immunotherapeutic protocols in the treatment and prevention of acute kidney graft rejection.

Provide support for basic studies in transplant immunology with the specific aim of defining the immune mechanisms involved in the rejection of organ transplants. These studies should provide important new information which should lead to the development of new drugs for immune suppression.

Bone Marrow Transplantation

A major NIAID initiative will be to support preclinical studies designed to obtain a better understanding of the basic mechanisms underlying graft-vs-host disease and the rejection of bone marrow grafts. These studies will aid in the development and design of new clinical trials,lead to an improvement in the prognosis of transplant patients and assist in the optimal utilization of the National Bone Marrow Registry.

NIAID plans to provide support for a program project to examine the potential of transplanting hematopoietic stem cells into the fetus to prevent the development of immune deficiency and hematologic diseases.

Provide support for collaborative studies between bone marrow transplant teams and basic immunologists to develop new protocols for the improvement of the success rates for unrelated bone marrow transplants.

Occupational Lung Disease

Develop improved methods for preparing extracts containing major wheat allergens.

Identify screening profiles that can be applied to current and prospective employees in industries associated with high incidence of OILD.

Develop treatment techniques for individuals with OILD who are unable to change jobs.

Continued banking of relevant chemicals conjugated to human serum albumin for diagnostic purposes will be encouraged.

Microbiology and Infectious Diseases

1991 Authorization: Indefinite

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$524,438,000	$561,338,000	+$36,900,000

Purpose and Method of Operation

Microbiology and Infectious Diseases supports extramural research to control diseases caused by virtually all infectious agents. The NIAID thus supports a wide spectrum of projects, ranging from basic studies of microbial physiology and antigenic structure, to collaborative clinical trials evaluating experimental drug and vaccines, to epidemiological studies.

Research areas in basic microbiology include molecular anatomy and function, genetics, biochemical composition, and physiological and biochemical processes. Studies on microbial pathogens extend such basic insights to identify immunizing antigens and to examine mechanisms of infection, pathogenicity, and virulence.

Research areas in virology include molecular structure, genetics, synthesis and reproduction, characterization of viral proteins and nucleic acids, mechanisms of pathogenicity, latency or persistence, reactivation, transformation, development of novel antiviral substances and of systems for growing unidentified agents, and protocols for identifying emerging pathogens. Basic information is being used to combat important viral disease such as influenza, genital herpes, hepatitis, and viral diarrheas.

Research on parasites involves similar basic approaches towards studying these far more complex multicellular organisms. In addition, studies are also directed toward controlling vectors.

The Program for the Accelerated Development of New Vaccines relies on recent advances in molecular biology, immunology, and their allied fields to develop new vaccines.

Rationale for the Budget Request

The FY 1991 budget estimate of $561,338,000 for microbiology and infectious diseases represents an increase of $36,900,000 or 6.6 percent over the FY 1990 estimate. Program plans for FY 1991 are concerned with the following major research areas: acute respiratory infections, particularly pertussis, influenza, and hepatitis; sexually transmitted diseases; systemic, persistent viral infections; other viral and bacterial diseases; parasitic diseases; and vaccine development. The following are initiatives NIAID will undertake in FY 1991 under the microbiology and infectious diseases program:

Bacterial Vaccines Program

Conduct studies to evaluate the ability of human hyperimmune IgG preparations to enhance vaccination in the prevention of Group B Streptococcus (GBS) disease in the newborn. It will be important to know that passive treatment with the hyperimmune globulin does not compromise active immunoprophylaxis when the two approaches are combined.

Encourage research in the field of synthetic peptide vaccine development, specifically as it relates to the production of an effective and safe carrier molecule, the definition of the specific immune response induced by these vaccines, and the effect of cell-mediated immunity responses.

Lyme disease

Lyme disease will continue to be considered an area of very high priority. Investigator-initiated research applications will continue to be encouraged.

The Institute anticipates receipt of at least two unsolicited applications for program projects devoted to the study of Lyme disease from major medical centers that are currently heavily involved in the treatment of patients suffering from Lyme disease.

Hepatitis

Expand in vitro evaluation for candidate HBV antivirals.

Encourage development of molecularly targeted HBV, HDV and HCV antivirals.

Promote basic research on the virus causing post-transfusion NANB, HCV, and how it causes disease as well as the development of prevention efforts.

Accelerated Development of Vaccines

Continue the development of improved acellular pertussis vaccines.

Continue the development of improved polysaccharide conjugate vaccines, particularly vaccines for pneumococcal and Hib disease.

Continue research on the malaria vaccines developed through recombinant DNA methods with a particular focus on generating candidate vaccines that contain antigens from the different stages of the parasites.

Continue to emphasize the development of improved adjuvants and particularly on the use of microencapsulation technology as an approach to immunization.

Continue to emphasize the development of improved influenza vaccines.

Continue to emphasize the development of attenuated or inactivated rotavirus vaccines.

Continue to emphasize and support basic research on host immune response, microbial determinants of virulence and pathogenesis.

Continue the development of live vectors for use in vaccines. Among the more promising are Salmonella, BCG, adenovirus, vaccinia, and poliovirus.

Haemophilus Influenzae type B

Continue studies on the mechanism of low antibody response to Hib polysaccharide among children who experience recurring episodes of invasive Hib disease.

Continue the development of new polysaccharide - based vaccines focusing efforts on:

- The size and forms of the polysaccharide used for immunization;
- The method for complexing polysaccharides to lipid and/or adjuvant molecules; and
- The route of administration of the polysaccharide-based vaccines.

Develop new strategies for overcoming immunological defects in native American Indians either by immunization or other interventions. Additional studies with conjugate vaccines will be needed to determine the ability to augment the immune response through a combined passive-active immunization approach.

Parasitic Diseases

Continued support for basic and applied research will emphasize the development of vaccines and new chemotherapeutic approaches for the control of parasitic diseases, as well as rapid and inexpensive diagnostic procedures that can be used in the field.

In the area of drug development, application of biochemical and molecular studies to the rational design of new chemotherapeutic agents and reversal of drug resistance will be emphasized. Field testing of newly developed diagnostic assays will be supported.

Pertussis

Continue research on the role of secretory mucosal antibodies in the development and maintenance of protection against B. pertussis.

Continue studies to determine how many of the toxins produced by B. pertussis directly interact with the host which will provide a useful model for the invasion of human cells by a variety of foreign molecules.

Compare the toxicity, as well as the structural and immunological responses, among recombinant forms of B. pertussis toxoids and the native toxin in experimental animal systems.

Pneumonia

Continue testing the safety, immunogenicity and efficacy of new candidate pneumococcal vaccines in appropriate populations.

Obtain and assess information regarding the incidence of pneumococcal disease in The Gambia in preparation for a possible Phase 3 study.

Continue the in vitro and animal model antiviral compound screening efforts against the respiratory viruses.

Emphasize the development of targeted antiviral drug approaches for the treatment of respiratory virus infections.

Influenza

Continue negotiations for the transfer of the ca influenza vaccine rights to private vaccine manufacturer(s) which would allow for the eventual licensing of this product. Assist the manufacturer(s) in the conduct of additional clinical studies required for licensure.

Continue supporting basic research in X-Ray crystallography and it's relationship to the development of targeted antiviral drugs.

Continue efforts focusing on the identification of the specific requirements for interspecies transmission of influenza viruses. Assist in obtaining samples of influenza virus in regions of the world in which there are close contact between man, ducks and pigs.

Antivirals, Immunology and Infectious Diseases excluding AIDS

Continuing and new clinical trials will evaluate experimental therapies for congenital CMV infections; disseminated zoster; localized zoster in normal, immunocompromised and AIDS patients; neonatal herpes; herpes encephalitis; and genital warts. The use of combination therapies and immunomodulators as components of combinations will receive increased emphasis.

Novel drug therapies and drug combinations will continue to be studied both in vitro and in animal models. Preclinical and clinical investigators will continue their close communication to ensure that preclinical antiviral programs are designed to provide optimal support for eventual clinical investigations.

Emphasize basic research on novel molecularly targeted approaches to the development of antiviral therapy.

Research on improved methods of drug delivery, and on the occurrence and clinical significance of virus mutants resistant to antiviral therapy.

Stimulate clinical trials to evaluate acyclovir therapy to prevent neonatal herpes infections and to treat pregnant women with severe genital herpes infections.

Chronic Fatigue Syndrome

Continue funding a comprehensive study of severely impaired patients which will include serial determinations of viral, immunologic, neurologic, cognitive and behavioral parameters. Results of this and other research projects will guide future extramural initiatives.

To follow-up on neuroendocrine findings reported in FY 1989, the NIAID patient cohort study will be expanded to include comprehensive measurements of immunologic function and mood over an extended time period.

Sexually Transmitted Diseases (STDs)

Continued support of basic and applied research for the prevention and control of STDs and their sequelae:

Vaccines - There are no vaccines for any STDs except hepatitis B. Efforts concentrating on the molecular immunology of protection and disease will continue to be enthusiastically supported.

PID - This serious health care problem will be the subject of a comprehensive workshop sponsored by the STD Programs of NIAID and CDC in September FY 1990. As recommended by the 1986 NIAID STD Study Group, a multi-center cohort study of sequelae of PID is being strongly considered to provide a better understanding of biological mechanisms and epidemiological factors which result in infertility, tubal pregnancy, chronic pelvic pain and recurrent infection.

Behavior - The STD Branch has given this issue high priority. A small workshop was held in November 1989, in preparation for a larger meeting in April FY 1990. The meetings are designed to define NIAID's role in behavioral research.

Diagnostics - Development of simple, accurate, inexpensive tests which are well-suited for resource-poor settings are critical. Towards this aim, an RFA has been issued in conjunction with the Antiviral Research Branch. In addition, the STD Branch and the Office of Health at the Agency for International Development will co-sponsor a workshop on this topic in February FY 1990.

AIDS-Related Issues - Studies that explore mechanisms by which genital ulcers and other STDs facilitate HIV transmission, as well as studies of the impact of HIV infection on the natural history, diagnosis, and treatment of other STDs will be actively encouraged.

STD Cooperative Research Centers (CRCs) - To augment STD research capacity, applications will be solicited in FY 1990 for establishment of STD CRCs. It is anticipated that this new approach will provide: (1) increased flexibility and speed of introduction of new research initiatives, (2) expansion of post-fellowship training and career development opportunities,

(3) a strong, visible clinical base for research activities through which involvement of both the local medical and lay communities can be built, and (4) greater opportunities for interaction and dialogue between STD investigators and NIAID staff.

National Institute of Allergy and Infectious Diseases

Intramural Research

1991 Authorization: Indefinite

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
656	$107,005,000	711	$115,603,000	+55	+$8,598,000

Purpose and Method of Operation

Basic research on problems in infection and immune diseases is performed by the 14 laboratories of the Division of Intramural Research (DIR) of the National Institute of Allergy and Infectious diseases (NIAID). The DIR is composed of over 800 tenured and non tenured scientists who work in these laboratories. Eleven of the laboratories are on the main campus in Bethesda, Maryland and in Frederick and Rockville, Maryland, three laboratories are located at the Rocky Mountain laboratories in Hamilton, Montana. NIAID clinical activities are housed in the NIH clinical center and consist of 50 inpatient beds and over 5,000 outpatient visits per year for the 133 clinical studies performed in the institute. The major focus of these laboratories is to investigate, through basic and clinical research, the causes of allergic, infectious and immunologic diseases which are major public health problems in the U.S. and internationally. In specialized areas of virology, microbiology, biochemistry, immunology, immunopathology, and immunogenetics, the intramural laboratories have emphasized research on AIDS, animal models of disease, drug therapy, disease prevention, vaccine development, Lyme disease, etiology of allergic diseases, and viral infections.

Rationale for the Budget Request

The FY 1991 budget request for intramural research is $115,603,000 which reflects an additional $8,598,006 or eight percent over FY 1990 for administrative and program increases. The request provides funds to continue the mission described above with major emphasis on vaccine development for several etiologic agents and for development of new methods to control the immune system that will be described below. As in the past five years, particular emphasis will be placed on research on AIDS, a disease with increasing prevalence both nationwide and worldwide. Care for these patients with AIDS continues to account for increasing amounts of the nation's health care budget. The following are the on-going activities and initiatives the NIAID will fund in intramural research activities in FY 1991:

Vaccine Development

Vaccines against viral and bacterial diseases have been improved or newly discovered using recently developed molecular biologic techniques.

NIAID scientists have discovered two genes in the Hepatitis A virus (the causative agent of infectious hepatitis) that regulate the growth of the virus. The isolation of these growth regulation genes, will permit growth of the virus in the laboratory. Laboratory propagation of the virus will facilitate efforts to produce a vaccine against this infection.

A naturally attenuated rotavirus infection of the intestine was uncovered when studying the causes of diarrhea in infants. Rotavirus is the causative agent for up to 50 percent of the 1 million diarrhea cases that occur in 1 to 4 year old American children. Worldwide, it is estimated that rotavirus is the causative agent in 9 million cases of diarrhea in children under the age of 5, and the cause of death of 873,000 infants per year. Multiple efforts have been made to rapidly develop a vaccine to prevent this disease. Four strains of rotavirus have been shown to cause diarrheal disease and a tetravalent vaccine developed by NIAID scientists is currently being evaluated in clinical trials. In other related studies, NIAID scientists have isolated a gene that regulates rotavirus virulence. This gene, which is called VP4, is being intensively investigated for its utility in developing an effective broad range rotavirus vaccine.

Using a recombinant baculovirus, NIAID scientists have produced two vaccines that are protective against Dengue infection in mice and monkeys. The system used was to insert a Dengue virus protein into a non virulent insect virus (baculovirus). Animals were then immunized with a recombinant virus protein produced by the baculovirus. In other studies a vaccine was made using a Dengue virus protein produced by another virus called vaccinia virus. The immunoprotective properties of the vaccines were proven when immunized animals demonstrated resistance to infection by the Dengue virus. These early results indicate that an effective vaccine may be produced and further research to accomplish this is underway.

Lyme Disease

Lyme disease is caused by a bacterial agent called *Borrelia burgdorferi* transmitted by ixodid ticks and is a growing infectious disease found in most of the U.S.. If the disease is detected early by serum testing, antibiotics can cure the disease. Unfortunately, up to 10 percent of the patients may be infected yet have negative serum tests. These undetected patients will eventually progress to advanced disease which may cause severe damage to the heart, brain and joints.

Scientists at the NIAID's Rocky Mountain laboratories have developed a sensitive assay for *B. burgdorferi* using the polymerase chain reaction. Initial laboratory tests indicate that this assay detects 99 percent of all infected patients. This greater sensitivity will aid clinicians in early diagnosis of Lyme disease. Current research is proceeding in improving the polymerase chain reaction technology so that a test kit can be commercially produced and used more widely.

Malaria Vaccine

Two major research advances in malaria research by NIAID scientists this year may facilitate development of an effective antimalarial vaccine. Vaccine development against malaria is complicated by the presence of four types of malaria, each with a complex life cycle. The most common type is *Plasmodium falciparum* which infects at least 100 million people worldwide and is responsible for at least 1 million deaths per year in Africa alone. Intensive research in malaria vaccines has been performed in order to assist international programs in controlling this major health threat.

The interaction of the malaria parasite with the immune system was studied and NIAID scientists found evidence that the parasite has lessened the level of the immune response against it by mimicking host molecular structures. This mimicry allows the malarial parasite to evade immune system attack and has been a stumbling block in developing a successful vaccine. Future studies will investigate the best recombinant vaccines against the different stages of the parasite and against the cellular receptor to which the malaria parasite binds.

Sexually Transmitted Diseases

NIAID scientists have identified the genetic mechanisms that control the pathogenicity of *Neisseria gonorrhea*, the cause of the sexually transmitted disease, gonorrhea (GC). Two surface proteins, the pilus protein and the outer membrane proteins, are critical to the virulence of GC infection. When the genes that code for these proteins are inactivated, the bacteria becomes non-virulent. Current research is directed towards further defining the biologic mechanisms that determine the virulence of *N. gonorrhea* and to develop candidates for vaccines.

Chlamydial infections are an underestimated cause of blindness, pneumonia, female pelvic infections (PID) and sterility. One epidemiologic study estimates that 500,000,000 people world wide are infected with chlamydia and in the U.S., 400,000 women have PID, thus suffering from preventable disease and sterility. One problem in controlling this infection is detecting it. Current technology uses fluorescence tests that are difficult to use, expensive, and not consistently sensitive enough for detection. Using knowledge obtained from structural studies of chlamydia, the polymerase chain reaction (PCR) has been adapted to detect infection with a sensitivity and specificity better than conventional assays. NIAID scientists working in the Rocky Mountain laboratories have also identified the parts of the chlamydia bacteria which the human immune system recognizes and then develops antibodies against. These proteins, named the major outer membrane proteins (MOMP), are being studied for vaccine efficacy.

Pertussis

Continued accomplishments have been made by NIAID scientist towards developing a vaccine against pertussis that is devoid of toxic side effects.

In FY 1989 the gene that codes for the S1 subunit of the toxin for pertussis, *Bordetella pertussis* was isolated and expressed in expression vectors, bacteria that are used as factories to produce gene products. The isolation of one of the most immunogenic parts of the bacterium without its toxic structure is a breakthrough that will allow the production of another effective and less toxic vaccine that may be used worldwide.

Herpes Infectious

There are multiple types of herpes viruses. NIAID clinical researchers have been able to show that different types of herpes infections have specific molecular and physical reasons for their different clinical presentations.

NIAID scientists have demonstrated by molecular biology techniques, that while these viruses are in their latent phase, the genetic function of the viruses is suppressed. Early work has identified genes in the virus that may regulate the ability of the virus to revert to latency. The improved understanding of the herpes viruses and their mechanism of activation should uncover new and more specific therapies against all types of herpes infection. In this regard, a new HSV-II vaccine for genital herpes is under study and a collaborative trial has begun to test a new antiviral drug, bromovinylarabinosyluridine (BvAra-U). BvAra-U is 1000 times more potent *in vitro* than acyclovir, the currently available anti viral drug.

AIDS RESEARCH

Animals Models

Animal models using cats and monkeys have been extensively used to understand the nature of the human HIV-1 virus. NIAID scientists have been working with simian immunodeficiency virus (SIV) and feline immunodeficiency virus (FIV) as parallel models for HIV infections in humans. The complete genetic sequences of FIV and SIV have been decoded and copies of these sequences will be inserted into laboratory cell cultures that are easily maintained. The creation of a stable cell culture study system will immensely increase studies of the genetic structure of the FIV and SIV viruses without the need for animal models. This will also enhance the ability to isolate factors that are important for understanding HIV in humans.

AIDS Vaccine Development

Vaccine and immunologic intervention studies are underway to investigate new areas of AIDS treatment. The gp160 vaccine has been tested successfully for initial efficacy and found to be immunogenic (causing an immune response in normal volunteers). The vaccine will be ready for use in prevention and control trials in high risk populations. Similarly, the use of innovative immune therapy techniques using recombinant CD4, (rCD4) with AZT will be tested in HIV positive patients to see if an antiviral drug in combination with an immunologic blocker will be effective. The CD4 molecule is a receptor to which the HIV-1 binds to the T-cell. When the site is blocked with the non-infectious rCD4 and anti-viral drugs are given simultaneously, therapy should be effective. This method of treating HIV infection will be intensively studied.

Viral Pathogenesis

NIAID scientists have found the HIV virus infects at least 10 to 100 times more T helper lymphocytes from patients with active AIDS, as compared to asymptomatic HIV positive patients. Using newer, more sensitive molecular biology assays developed by NIAID scientists, the HIV lymphocyte infection rate was found to be 1 infected lymphocyte for every 10 to 100 thousand uninfected lymphocytes in asymptomatic, HIV positive patients. In patients who develop symptoms of AIDS, the rate of HIV infected lymphocytes increases to 1 infected cell for every 100 uninfected cells. The progression of virus replication and cell infection correlates with a rapid decrease of T-helper (CD-4) cells which are critical to a functional immune system. This finding emphasizes the need to treat HIV patients early before an accelerated viral replication state develops resulting in the destruction of their immune system.

International Research

NIAID experience with heterosexually transmitted AIDS is extensive and is a result of its international research effort in Zaire. Since 1984, NIAID's operation in Zaire, Project SIDA, has performed over 60 studies on the nature of heterosexually transmitted HIV infection. The similarities of AIDS in Zaire and in the U.S. is striking. It has been proven in both Zairian and American studies that health workers do not have an abnormally high risk of acquiring HIV secondary to their work. Studies of sexually active males and females in African cities have shown that sexually transmitted diseases and other cofactors are important for accelerating the spread of HIV. The association between sexually transmitted diseases and the increased risk of acquiring AIDS was noted two years ago in Zaire, is currently being seen in the U.S.. Behavior interventions, clinical treatments and other studies are on going in Zaire to help adult and pediatric populations in the U.S. and abroad.

Bone Marrow transplantation

The establishment of a bone marrow transplantation unit is planned to perform experimental transplants on patients with diseases responsive to genetic therapy. Thalassemias (anemias caused by defective hemoglobin) and chronic granulomatous disease are two genetically inherited diseases that can be corrected by gene therapy. The primary objective of the unit will be to provide a site where new experimental gene therapies can be done on the NIH campus and allow rapid evaluation of treatments that will be essential for medical treatment of a number of genetically inherited diseases.

SCID and transgenic mice

A major expansion of mouse models is planned to allow in depth research on the immunologic and genetic characteristics of infection and allergic diseases. Efforts will be concentrated on severe combined immunodeficiency mice (SCID) and transgenic mice. Laboratory bred SCID mice do not have a functional immune system. For this reason, human cells, i.e. T-lymphocytes, can be maintained in these mice. This will permit NIAID scientists to evaluate the effect of vaccines on human cells, the effect of drugs on infected human cells and the efficacy of new genetic therapeutic modalities.

New retroviral vaccine research

The retroviral core protein, p24, will be evaluated as a vaccine candidate using recombinant vaccinia virus systems. The p24 protein is the earliest recognized viral protein by the immune system of an HIV infected patient. NIAID scientists plan to insert the non infectious core protein of HIV into a vaccinia virus and evaluate its protective efficacy in animal models. NIAID scientists have started studies to examine the feasibility of directly controlling the HIV genetic coding as a method for treatment. The regulatory regions of different viruses and cells will be inserted into the regulatory region of the HIV virus genome and evaluated for efficacy in diminishing or eliminating the virulence of the HIV virus. Previous research on viruses have demonstrated that specific genes within the HIV genome control its ability to infect patient cells. It will be determined which regulatory gene insertions are most effective in making HIV non virulent in vitro.

Gene therapy unit

The gene therapy unit in the NIAID has been formed to investigate the potential for genetic treatment for inherited or acquired human diseases. Recent advances in our understanding of molecular biology will permit researchers to develop methodologies for changing the genetic coding of defective genes in human cells or blocking infectious agents from entering cells. For example, the genetic transmission of chronic granulomatous disease has been recently elucidated by NIAID scientists. This discovery permits scientists to design genetic therapies to correct the genetic defect.

National Institute of Allergy and Infectious Diseases

Research Management and Support

1991 Authorization: Indefinite

Obligational Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
377	$39,467,000	405	$42,674,000	+28	+ $3,207,000

Purpose and Method of Operation

This activity provides the funds and positions that support the overall management and policy direction of the Institute, as well as the full range of scientific and administrative management of the Institute's extramural programs. Included are a wide variety of managerial, scientific, and administrative functions ranging from scientific review and award and processing functions for research grants and contract to administrative support and informational services.

The Office of the Director has primary responsibility for policy development and planning. Administrative and managerial staff are organizationally located within this Office and other staff offices, while program scientific staff are divided among the four major extramural programs: Acquired Immunodeficiency Syndrome; Microbiology and Infectious Diseases; Allergy, Immunology, and Transplantation; and Extramural Activities. These programs focus their efforts on reviewing, awarding and administering grants and contracts to universities, medical schools, and other research organizations, providing guidance on scientific programs and projects, and ensuring the dissemination of research results produced by these projects to the scientific community and the public.

Rationale for the Budget Request

The FY 1991 budget request for research management and support is $42,674,000, an increase of $3,207,000 or 8 percent over the FY 1990 level of $39,467,000. Major activities to be supported during FY 1991 include:

Continuation of support for and participation in planning, evaluation and stimulation of research on Acquired Immunodeficiency Syndrome (AIDS). Efforts will include continued participation by NIAID senior staff in the Public Health Service Task Force on AIDS and NIH AIDS Executive Committee.

Emphasis will be placed on supporting laboratory and epidemiologic research on AIDS, as well as sponsorship of selected meetings and conferences on high priority AIDS research topics and issues, including areas of technology transfer and consensus development.

Emphasis will be placed on keeping abreast of state-of-the-art automated data processing (ADP). Continuation of refinements and improvements to the Institute's ADP system. Efforts will be focused on the review and testing of improved and new software packages which will enhance and improve upon those currently used, and the introduction of select new hardware which will enhance the effectiveness and efficiency of the current system.

Continuation of efforts to reassess the state of science in those areas within the Institute's purview. These efforts include the review of progress and the identification of areas of unusual scientific opportunity which may lead to new approaches to support and facilitate research.

Efforts will continue to refine the Institute's planning and analysis functions. One goal will be the consolidation into one system various review and planning exercises which were previously performed separately. Such a system, combined with improve methods of analyzing data on ongoing and future research initiatives will make the overall planning process more efficient and effective.

Maintenance and expansion, as needed, of various service contracts which support the Office and of the Director and the Extramural Programs. These services include typing support, mail and messenger service, and logistical support for conferences, meetings and workshops.

Continuation of efforts to ensure internal control through established processes and procedures. Reviews of productivity will continue to be made in selected functional areas within the Institute.

Maintenance of the established multi-media information dissemination activities. These activities focus on all of the numerous diseases and disorders of concern and interest to the Institute, and emphasize outreach and are directed to health professionals and voluntary associations, as well as with the various private sector elements that reach selected target audiences or at-risk groups.

Support for task forces and outside advisory groups which assist the NIAID in defining scientific opportunities and setting priorities will be continued. The Institute will also continue to sponsor selected meetings, conferences, workshops, and symposia on high-priority research topics and issues, including areas of technology transfer and consensus development.

Continued sponsorship and support for ongoing and selected new collaborative research efforts with scientists in developing countries on basic and clinical research on diseases of international importance. These collaborations stimulate biomedical research in specific disease categories of interest to the Institute, with the goal of decreasing the morbidity and mortality rates in these countries.

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Detail of Permanent Positions

	1989 Actual	1990 Appropriation	1991 Estimate
ES-4	7	7	7
ES-3	1	1	1
ES-2	3	3	3
ES-1	1	1	1
Subtotal	12	12	12
GS/GM-15	37	40	40
GS/GM-14	43	50	51
GS/GM-13	22	34	38
GS-12	48	58	61
GS-11	79	98	105
GS-10	5	5	5
GS-9	82	102	109
GS-8	18	22	22
GS-7	70	88	93
GS-6	70	84	88
GS-5	67	80	85
GS-4	24	29	29
GS-3	2	2	2
GS-2	1	1	1
Subtotal	568	693	729
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant surgeon General grade	--	--	--
Director grade	38	41	41
Senior grade	14	15	15
Full grade	1	4	4
Senior assistant grade	1	1	1
Assistant grade	--	--	--
Subtotal	54	61	61
Ungraded	36	36	36
Total permanent positions	670	802	838
Unfilled positions, end-of-year	--	--	--
Total permanent employment end-of-year	670	802	838

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

New Positions Requested

	Grade	Number	Annual Salary
NIAID Intramural Program			
Pharmacokineticist	14	1	$52,104
Medical Officer	13	1	44,092
Molecular Biologist	13	2	88,184
Virologist	13	1	44,092
Biologist	11	4	123,749
Biologist	9	5	127,848
Laboratory Technicians	5	3	50,627
		17	530,696
NIAID Research Management and Support			
Health Specialist	12	3	111,237
Health Specialist	11	3	92,812
Program Analyst	9	2	51,139
Statisitical Assistant	7	1	20,195
Purchasing Agents	7	3	60,585
Secretary	7	1	21,598
Grants Clerk	6	2	37,620
Secretary	6	2	40,129
Clerk Typist	5	2	37,130
		19	472,445

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

Advisory and Assistance Services

The increase of the FY 1990 consultant services request is due solely to an increase in Committee meetings. The Board of Scientific Counselors meet twice a year to evaluate and advise the Intramural Research program. Due to scheduling problems, the Board only met once in FY 1989, however, two meetings are planned in FY 1990. The Extramural program has initiated a newly chartered AIDS Research Advisory Committee. The Committee is comprised of three Subcommittees (AIDS Liaison Subcommittee, AIDS Basic Research Subcommittee, and AIDS Clinical Research Subcommittee) which will advise and support the Director of the Division of AIDS, on programs directed at finding new and improved methods of diagnosing, treating and preventing HIV related diseases. The three Subcommittees will meet a total of 17 times during the fiscal year.

WEDNESDAY, MARCH 14, 1990.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

WITNESSES

RUTH L. KIRSCHSTEIN, DIRECTOR
WILLIAM F. RAUB, ACTING DIRECTOR, NIH
MARVIN CASSMAN, DEPUTY DIRECTOR, NIGMS
WILLIAM T. FITZSIMMONS, EXECUTIVE OFFICER, NIGMS
G. EARL HODGKINS, FINANCIAL MANAGEMENT OFFICER, NIGMS
W. SUE SHAFER, ASSOCIATE DIRECTOR FOR PROGRAM ACTIVITIES, NIGMS
DENNIS P. WILLIAMS, DEPUTY ASSISTANT SECRETARY, BUDGET, DHHS

Mr. NATCHER. We take up next the National Institute of General Medical Sciences.

We have before the committee at this time, Dr. Ruth E. Kirschstein. Dr. Kirschstein, it is a pleasure to have you back before the committee. You have appeared before our subcommittee on a number of occasions. It is always a pleasure to have you.

Dr. KIRSCHSTEIN. Thank you, Mr. Chairman.

Mr. NATCHER. Before you give us your statement, tell us who you have with you there at the table, please.

Dr. KIRSCHSTEIN. Thank you, Mr. Chairman. I would like to introduce my colleagues. On the far left is Dr. W. Sue Shafer, the Associate Director of the Institute. Next to her, Mr. Earl Hodgkins, who is the Financial Management Officer. Next to him, Mr. William Fitzsimmons, the Executive Officer.

On my far right, Mr. Dennis Williams, then Dr. Raub, and next to me on my immediate right, Dr. Marvin Cassman, the Deputy Director of the Institute.

Mr. NATCHER. Thank you, Dr. Kirschstein.

Now, we will be pleased to hear from you.

OPENING STATEMENT

Dr. KIRSCHSTEIN. Mr. Chairman, members of the committee, it is a particular pleasure for me to appear before you this year to tell you that two of the most prestigious biomedical research prizes have been awarded to grantees of the National Institute of General Medical Sciences. The 1989 Nobel Prize in chemistry was awarded to Doctors Thomas Cech of the University of Colorado at Boulder, and Sidney Altman of Yale University.

The 1989 Lasker Award for basic biomedical research was shared with three other people by Dr. Alfred Gilman of the University of Texas, Southwestern Medical Center. The revolutionary discovery, and it truly is, by Doctors Cech and Altman, that ribonucleic acid, RNA, which was long thought only to carry genetic messages, can also act as a biochemical catalyst has led, in a very short period of time, to the possibility of very important practical applications.

For example, attempts are underway to develop a technique using these RNA enzymes or ribozymes as a means of blocking the activity of the human immunodeficiency or AIDS virus, about which you heard from Dr. Fauci. The discoveries by Doctors Cech and Altman and also Dr. Gilman signify a phenomenon that is very important in basic research, the coming together of chemistry and biology in the basic studies that are the hallmark of the NIGMS-supported research. These studies are of great importance to improving not only the well-being of the people of the United States, but also the economic and competitive well-being of this country in world markets.

In preparing for its future, the United States must be cognizant of economic and demographic imperatives; namely, that, by the year 2000, one-third of the new entrants into the work force, including biomedical researchers, will be minorities. We in NIGMS now have a unique opportunity to help assure that there will be a group of well-prepared minority biomedical researchers, since, beginning in fiscal year 1990, both the Minority Access to Research Careers Program and the Minority Biomedical Research Support Program will be residing in this Institute.

NIGMS has a critical role to play in all research training, particularly through its highly successful Medical Scientist Training Program, the combined M.D.-Ph.D. degree granting program. The rapidly growing biotechnology industry will continue to rely, in the future, on well-trained scientists, and the recently established NIGMS Biotechnology Research Training Program can be expected to play an increasingly vital role in the continued commercialization of important scientific discoveries.

On the basis of the current progress of the grantees of the National Institute of General Medical Sciences, and with the continued training of new young scientists to do research, I am confident that the quality of the superb achievements that I have presented to you today will continue.

The fiscal year 1991 budget request for the Institute's research and research training programs totals $745,494,000. I will be submitting my longer statement for the record, and I would be pleased to answer any questions that you and other members of the committee may have.

[The information follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institute of General Medical Sciences

It is an honor for me to appear again before this committee, to present the outstanding programs and accomplishments of the National Institute of General Medical Sciences (NIGMS). This year, it is a particular pleasure to tell you that, as so often in past years, two of the most prestigious biomedical research prizes have been awarded to NIGMS grantees. The 1989 Nobel Prize in chemistry was awarded to Drs. Thomas Cech of the University of Colorado at Boulder and Sidney Altman of Yale University and the 1989 Lasker Award for Basic Medical Research was shared, with three others, by Dr. Alfred Gilman of the University of Texas Southwestern Medical Center.

The discovery, by Drs. Cech and Altman, that ribonucleic acid (RNA), long thought only to carry genetic messages, can also act as a biochemical catalyst, or enzyme, came as a complete surprise. This revolutionary finding has led to the coining of a new term in biology, "ribozyme" or RNA enzyme. Ribozymes are not just curiosities of nature. In just eight years since their discovery, scientists are already thinking of some very important practical applications. Indeed, a number of university laboratories and biotechnology companies now are making what are being called "designer ribozymes," RNA enzymes tailored to catalyze very specific reactions. For example, attempts are underway to develop a ribozyme designed to block the activity of the human immunodeficiency or AIDS virus.

Dr. Alfred Gilman of the Department of Pharmacology, University of Texas, Southwestern Medical Center, the recipient of the Lasker Award, discovered a family of proteins known as the G proteins. G proteins have been recognized to be integral to the transmission of signals into and within cells. If there is disruption of G protein activity, cells malfunction and several specific diseases may result. For example, the toxin produced by the bacteria that cause pertussis is known to act by disrupting the binding of one of the G proteins to the cells of the lungs, thereby causing the symptoms we all recognize as whooping cough. A different toxin, produced by the cholera bacteria, results in the persistent, abnormal activation of another G protein in the cells lining the intestinal tract, causing the tremendous loss of fluid in that disease, a loss which can lead to prostration and, often, death. Abnormalities of G proteins have also been implicated in some forms of cancer.

This remarkable work combines physiology, pharmacology, molecular biology and, again, chemistry. Dr. Gilman's broad background and training enabled him to move from discipline to discipline as the scientific opportunities arose. He has a combined M.D.-Ph.D. degree from Case-Western Reserve Medical School in a program that was a predecessor to the highly successful Medical Scientist Training Program now funded by NIGMS. Dr. Gilman was a graduate of the small, but outstanding, NIGMS intramural research training activity, the

Pharmacology Research Associate Training Program. We have just learned that he will also be the 1990 recipient of the highly regarded Passano Award.

The enormous significance to the field of biomedical research of these two discoveries, RNA enzymes and G proteins, is obvious. Together they signify the congruence and melding of the fundamental, undifferentiated research endeavors that are the hallmarks of support of the National Institute of General Medical Sciences. This "coming together" of the basic research areas of biology and chemistry is of great importance to improving not only the well-being of the people of the United States, but also of the economic and competitive status of this country in world markets.

Another important example of the "coming together" of synthetic chemistry and biology is the work of Dr. E. J. Corey of Harvard University, a long-time NIGMS grantee, who has coined another new term, "chemzymes," for the unique synthetic catalysts or enzymes that he has developed. These chemzymes are small, totally synthetic molecules, whose design is based on a rational analysis of molecular structure. These designer chemzymes can distinguish molecules in a solution as being either "left-handed" or "right-handed" and choose the one to which the fit is best, like a left-hand glove which will only fit on a left hand. This ability to selectively recognize only the active molecules makes the action of chemzymes extremely efficient. A chemzyme, for example, can be tailor-made to facilitate binding of a drug to a virally infected cell. As might be expected, pharmaceutical manufacturers have quickly developed collaborations with the Harvard chemists. Important new therapeutic entities now are being developed using this approach to rational chemical synthesis.

The combined techniques of molecular biology, chemistry and structural biology are being used to identify and characterize the subunits of the cell, each of which is essential to its normal functioning. Of particular importance is the cell's surface membrane which basically serves to confine the contents of the cell, allow intercellular communication and permit messages to enter or leave the cell. Some cells have special receptor molecules in their surface membranes. For example, the cells that line blood vessels have receptors or "adhesion molecules" which allow circulating white blood cells, such as lymphocytes, to adhere to the vessel lining, migrate through the vessel wall and then seek out inflamed or injured tissues. In some cases, this permits the control of infections. In others, burn injuries may more rapidly heal because these white blood cells are able to reach the burned tissue rapidly and allow the repair process to begin. The work of NIGMS grantees in the biochemical identification and characterization of these adhesion molecules has enormous implications for the prevention of the spread of cancer cells, for the treatment of cancers that already have spread, and for the design of therapeutic substances that can be targeted to diseased tissues.

In another area of research, biophysics, I would note that the Institute's grantees have made excellent progress in elucidating the three-dimensional structures of a number of biologically important proteins and other macromolecules. This year, biophysicists, working with support from NIGMS, have begun to make significant advances in determining the specific three-dimensional structures of some of the proteins important to the activity of the human immunodeficiency virus. These advances have enabled other scientists to begin to design chemicals or drugs which take advantage of the structural features to inhibit AIDS infection. This line of attack against this dread viral infection, like those I mentioned earlier, again illustrates the intersection of the chemical and pharmacological sciences with the physical sciences, and molecular biology.

As the chemical, physical and biological sciences become more and more interactive, the need for extremely well-prepared researchers in a wide range of areas is more and more apparent. The NIGMS research training programs have long stressed interdisciplinary preparation of new young scientists. Leading researchers like Drs. Cech, Altman, Gilman, and Corey, are deeply involved in training such young people for future careers in research. While many of the remarkable advances which I have described herald the possibility of devising new strategies for diagnosis and therapy, they also raise a host of new questions which still must be addressed. To find the answers, this country needs a constant influx of skilled new research talent. The multidisciplinary research training programs of NIGMS are essential in the preparation of such highly qualified scientists, the very life-blood of future biomedical research progress.

But, in preparing for the future, the United States must be cognizant of the economic and demographic imperatives, namely, that, by the year 2000, one-third of the new entrants into the work force, including biomedical researchers, will be minorities. The NIGMS now has a unique opportunity to help assure that there will be a group of well-prepared minority biomedical researchers. With the beginning of Fiscal Year 1990, both the Minority Access to Research Careers (MARC) and the Minority Biomedical Research Support (MBRS) Programs reside in this Institute. Thus, NIGMS has the primary responsibility at NIH for such activities. Recognizing the importance of this responsibility, we have begun the process of improving coordination between the two programs, while keeping their distinct goals intact. During the past year, we had extremely successful meetings of the directors, the faculty and the students of each of the two programs. Dr. Louis Sullivan, Secretary of the Department of Health and Human Services, spoke at these meetings, serving as a role model and a source of inspiration to the students and their preceptors. In addition, the NIGMS is now supporting 24 minority undergraduate and graduate students, using administrative supplements to regular research grants to provide for their research training. All these efforts, along with a possible extension of the MARC Program to include honors students in the beginning years of college, indicate our commitment to the future role of minority biomedical researchers.

In addition, there are other essential areas of research training in which NIGMS has a critical role. For example, the need for physician-researchers throughout the United States makes the highly successful Medical Scientist Training Program, the combined M.D.-Ph.D. degree granting program, one of increasing importance. The example of Dr. Gilman's success as a pre-eminent physician-researcher is an inspiration to trainees in this program.

The rapidly growing biotechnology industry, in the future, will continue to rely on the work of well-trained scientists, like Drs. Gilman, Altman, Cech, and Corey, for the basic biomedical research discoveries that permit the production of important vaccines, antitoxins, drugs, and chemicals to treat and diagnose the diseases that still afflict mankind. This is why the recently started NIGMS biotechnology research training program can be expected to play an increasingly vital role in the continued commercialization of important scientific discoveries.

Clearly, the non-targeted research supported by NIGMS has opened up new vistas and produced new theories and concepts, but it also has had remarkable success in leading to new diagnostic and therapeutic opportunities. The challenges of uncovering the secrets of life and of elucidating the underlying causes of the still numerous diseases of man that are not yet understood are very great indeed. On the basis of current progress and with the continued training of new young scientists to do research, I am confident that the quality of the NIGMS-supported basic research of the future will be even better than the superb scientific achievements that I have presented to you today.

Mr. Chairman, the FY 1991 budget request for the Institute's research and research training programs is $745,494,000. I would be pleased to answer any questions you may have.

KIRSCHSTEIN, DR. RUTH L.
Director, National Institute of General Medical Sciences

October 12, 1926. Brooklyn, New York

Education: A.B., magna cum laude, Long Island University, 1947. M.D., Tulane University School of Medicine, 1951.

Professional History: 1951-52, Internship, Medicine and Surgery, Kings County Hospital, Brooklyn, N.Y. 1952, Assistant Resident, Pathology, Veterans Administration Hospital, Chamblee, GA. 1952-54, Resident, Pathology, Providence Hospital, Detroit, MI. 1954-55, Trainee of National Heart Institute and Instructor in Pathology, Tulane University School of Medicine. 1956-57, Medical Officer, Resident in Pathology, Clinical Pathology, Clinical Center, NIH. 1957, Medical Specialty Board Certification, Pathology (anatomic and clinical pathology). 1957-60, Medical Officer, Pathologist, Laboratory of Viral Products, DBS, NIH. 1960-62, Chief, Section of Pathology, Laboratory of Viral Immunology, DBS, NIH. 1962-64, Assistant Chief, Laboratory of Viral Immunology and Chief, Section of Pathology, DBS, NIH. 1964-65, Acting Chief, Laboratory of Pathology, DBS, NIH. 1965-72, Chief, Laboratory of Pathology, DBS, NIH. 1971-72, Assistant Director, Division of Biologics Standards, NIH. 1972-73, Acting Deputy Director, Bureau of Biologics, FDA. 1973-74, Deputy Associate Commissioner for Science, FDA. 1974-present, Director, National Institute of General Medical Sciences, NIH.

Professional Organizations: American Association of Immunologists; American Association of Pathologists; American Society for Microbiology; Institute of Medicine, National Academy of Sciences.

Committee Memberships: Invited member of World Health Organization Expert Group on International Requirements for Biological Substances; Geneva, Switzerland, 1965 & 1971. Chairperson, NIH Grants Peer Review Study Team, 1975-76. Chairperson, PHS Genetics Coordinating Committee, 1976-79. Member, Fogarty International Center Scholars-in-Residence Advisory Committee, 1977-82. Chairperson, PHS Task Force on Women's Health Issues, 1983-84. Chairperson, PHS Coordinating Committee on Women's Health Issues, 1984-present. Member, NIH Advisory Committee for the IOM Study of the Organizational Structure of the NIH, 1983-84. Member, NIH Peer Review Committee, 1987-88. Member, HHS Executive Development Board, 1985-present. Member, Federal Task Force on Women, Minorities and the Handicapped in Science and Technology, 1987-present.

Honors, Awards: Elected to Institute of Medicine, National Academy of Sciences, 1982. Doctor of Science, Honoris Causa, The Mount Sinai School of Medicine, 1984. Honorary Doctor of Laws, Atlanta University, 1985. Presidential Meritorious Executive Rank Award, 1980. PHS Equal Opportunity Achievement Award, 1983. PHS Special Recognition Award--group award to PHS Task Force on Women's Health Issues (Chairperson), 1985. Distinguished Executive Service Award of the Senior Executive Association, 1985. Presidential Distinguished Executive Rank Award, 1985. Honorary Doctor of Science, Medical College of Ohio, 1986.

RESEARCH TRAINING BUDGET

Mr. **Natcher**. Thank you, Dr. Kirschstein.

We hear of the great need for increases in NIH research training. Dr. Kirschstein, tell us why, then, are all of your research training efforts except the minority access program frozen at the 1990 level?

Dr. **Kirschstein**. Mr. Chairman, within the constraints of the fiscal year 1991 budget, certain decisions had to be made. Although we agree with you completely that there is a great need for research training in all areas, we were unable to increase the numbers of trainees in the more traditional areas of research training.

Based on the demographic and economic considerations that I mentioned in my opening statement, we were, however, pleased to be able to increase research training efforts in the minority programs.

NATIONAL ACADEMY OF SCIENCES RESEARCH MANPOWER REPORT

Mr. **Natcher**. If you will, clarify for us the recommendations of the new National Academy of Sciences report regarding the number of research trainees supported by the National Institutes of Health.

Dr. **Kirschstein**. Mr. Chairman, as you know, since 1975, the National Research Service Act has asked that the Institute of Medicine, through its manpower committee, provide information and do studies regarding the needs for research manpower in biomedical sciences.

A number of reports have been submitted by that committee over the years; the most recent one was issued in December of 1989.

In that report, which was the first one in four years, the committee determined the number of trainees that it felt would be required in each of the coming years, through 1995. There was a change, however, in the way in which the committee reported these numbers. It decided to report them as full-time equivalents rather than as individual trainees as it had in the past. The committee felt that the decision to use full-time equivalents would reflect what happens in practicality at many universities. At those schools, individuals can be appointed on training grants or activate fellowships at any time throughout the year. Therefore they do not necessarily serve for a full 12-month period.

Thus, it was the committee's decision to recommend the numbers of trainees it feels are needed in this way. Actually full-time equivalents are about 85 percent of the total number of individual trainees, so that the numbers reported by the National Academy of Sciences, if multiplied by 1.15, would be comparable to the way the numbers were reported in the past by the committee.

I have actually prepared information which correlates those numbers with the way we, at NIH, report trainee slots in our budgetary documents. In discussions with some of your staff I have provided that information and would be happy to provide it if you wish, for the record.

[The information follows:]

PHS Research Training

Translation of Institute of Medicine/National Academy of Sciences Recommendations – Research Trainees/FTEs to Positions*
(NIH Is Approximately 90% of Total)

		Recommended					
		FY 90	FY 91	FY 92	FY 93	FY 94	FY 95
Biomedical	Pos.	9,430	9,890	10,350	10,810	10,810	10,810
	FTEs	8,200	8,600	9,000	9,400	9,400	9,400
Predoctoral	Pos.	4,945	5,290	5,635	5,980	5,980	5,980
	FTEs	4,300	4,600	4,900	5,200	5,200	5,200
Postdoctoral	Pos.	4,485	4,600	4,715	4,830	4,830	4,830
	FTEs	3,900	4,000	4,100	4,200	4,200	4,200
Behavioral	Pos.	1,058	1,058	1,058	1,058	1,058	1,058
	FTEs	920	920	920	920	920	920
Clinical	Pos.	2,473	2,473	2,473	2,473	2,473	2,473
	FTEs	2,150	2,150	2,150	2,150	2,150	2,150
MSTP	Pos.	736	736	736	736	736	736
	FTEs	640	640	640	640	640	640
All Other	Pos.	1,737	1,737	1,737	1,737	1,737	1,737
	FTEs	1,510	1,510	1,510	1,510	1,510	1,510
TOTAL	Pos.	12,961	13,421	13,881	14,341	14,341	14,341
	FTEs	11,270	11,670	12,070	12,470	12,470	12,470
Estimated NIH Share of Total	Pos.	11,664	12,078	12,492	12,906	12,906	12,906
	FTEs	10,143	10,503	10,863	11,223	11,223	11,223
Estimated NIGMS Share of Predoctoral	Pos.	2,967	3,174	3,381	3,588	[illegible]88	3,588
	FTEs	2,580	2,760	2,940	3,120	3,120	3,120

* Positions equal 115% of FTEs.

NUMBER OF PREDOCTORAL TRAINEES

Mr. NATCHER. Now, Dr. Kirschstein, how does this compare with the number of trainees in your 1991 request?

Dr. KIRSCHSTEIN. The number of graduate students or trainees seeking the traditional Ph.D. in the NIGMS request is 2,050. I will stress predoctoral training, because that is the area in which NIGMS has the largest investment and it is this Institute at NIH which supports the vast majority of predoctoral training. While the number requested in the budget is 2,050, the National Academy of Sciences report recommends 2,900 trainees in the type of predoctoral training that NIGMS should be supporting. That means there would be a shortfall of a little over 800 trainees.

BIOTECHNOLOGY TRAINING

Mr. NATCHER. The major source of research growth, as you know, is projected to be in private industry. Do you think, Dr. Kirschstein, that industry should take a larger role in financing research training since it stands to reap much of the benefit?

Dr. KIRSCHSTEIN. Mr. Chairman, we have been working with the biotechnology industry to try to share some of the training efforts. We believe that for the biotechnology industry to be successful, there needs to be considerable training support, both from the Federal and State governments as well as from industry.

That is why, two years ago, we established the Biotechnology Research Training Program, which prepares young men and women to become highly qualified to do research in basic areas, and then apply that research in the biotechnology industry. These training grants are designed to have the trainees spend time in laboratories, both in academia and in the biotechnology industry.

Mr. NATCHER. Now, Dr. Kirschstein, how much funding and how many research trainees are you requesting for the new biotechnology program?

Dr. KIRSCHSTEIN. For the new biotechnology training program, in fiscal year 1991, we are requesting $4,256,000 for 190 trainees.

Mr. NATCHER. How does this compare, Dr. Kirschstein, with the recommendation of the advisory group that you consulted with a couple of years ago?

Dr. KIRSCHSTEIN. Yes, Mr. Chairman. We brought a group of experts together several years ago when Members of the Congress evinced considerable interest in having NIGMS develop a biotechnology research program. That group provided us with a five-year plan, which suggested that, in the first year, which was fiscal year 1989, we should support 250 trainees; in the second year, 1990, 500 trainees; and in the third year, 1991, 750 trainees.

We are currently able to support only 190 trainees in 1991, so we are very far behind.

DEVELOPMENT OF RESEARCHERS

Mr. NATCHER. What steps can NIH take to improve the share of the research trainees who eventually apply for research grants, Dr. Kirschstein?

Dr. KIRSCHSTEIN. Mr. Chairman, research trainees can be divided into two groups. One group are the individuals who, through their training, receive a graduate, that is, a Ph.D. degree. That is a research degree, and those individuals in very large numbers, in excess certainly of 90 percent, do indeed go into the research and attempt to get NIH research grants after receiving postdoctoral training. They are, in general, quite successful.

The other group are the trainees who take postdoctoral training after their medical degree, the M.D. degree. Those individuals have not been as active in seeking research grants. This phenomenon receives a good deal of discussion in the report that emerged from a set of task forces that Dr. Lenfant, Dr. Kupfer and I headed at Dr. Wyngaarden's request.

Among the recommendations of those task forces was one aimed at changing some of the training activities for physicians to assure that their training period be at least two years, or perhaps longer, and in addition, to have that research training period integrated with their clinical training, their residency training. Another recommendation was to provide them with the opportunity, after both their research and residency training are finished, to receive immediately a career development, physician-scientist grant.

One of the reasons that physicians do not pursue research careers is that during their postdoctoral research training they have not been remunerated in a fashion consistent with their clinical training. This is at least one factor in their discouragement from pursuing research careers.

Mr. NATCHER. Mr. Conte, I yield to you.

MEDICAL SCIENTIST TRAINING PROGRAM

Mr. CONTE. Thank you, Mr. Chairman.

Doctor, it is a pleasure to have you before our committee. I should start out by saying that I want to take this opportunity to welcome my dear and beloved friend to our committee.

You have done a top-notch job in making your Institute world-famous, you are doing the nuts and bolts research which underlies all medical progress, and I want you to know how appreciative we are in having you come before our committee today.

Doctor, the National Academy of Sciences recently issued a report which stated that while the country has plenty of M.D.s, we still need more physician scientists. I am pushing for the Senior Biomedical Research Service, I would like to see if we can't help your program produce more top-notch young physician investigators.

To what extent does the Medical Scientist Training Program, administered by your Institute, deal with this problem, and how successful have the graduates been in the biomedical research?

Dr. KIRSCHSTEIN. Mr. Conte, because we, in NIGMS, have for many years agreed that there is a great need for physicians who are well-trained in research, we started a program in 1964 called the Medical Scientist Training Program. This is a program which integrates the training for the M.D. degree, with the research training required to obtain the research or Ph.D. degree. It is a combined M.D.-Ph.D. program. That program has grown from three schools, which were supported in 1964, to 29 schools today.

In 1964, there were 17 trainees; today, there are 735 trainees. Approximately 100 of these M.D.-Ph.D.s graduate each year. These individuals are uniquely qualified to do research in areas that bridge the gap between basic and clinical research, and they are remarkably successful in obtaining research support and are doing the cutting-edge research.

The Program has had several graduates over the years who are now members of the National Academy of Sciences. A large number of the program's graduates are full professors in the medical schools of the country, and 88 percent of them are performing research.

Mr. CONTE. How many trainees will you support in 1991?

Dr. KIRSCHSTEIN. Seven hundred and thirty-five.

Mr. CONTE. Is that about the right number?

Dr. KIRSCHSTEIN. That is the number that we have been attempting to reach for some years, and which the National Academy of Sciences had recommended in the past. Based on our recent assessment of this program, in our professional judgment, that number could increase in fiscal year 1991 to 800, and would really help address the need for physicians who are well-trained in research.

SUPPORT FOR BASIC RESEARCH

Mr. CONTE. Very good.

The President's budget also states that Federal support for basic research is being increased 8 percent over 1990. However, your Institute's budget is being increased less than 5 percent over 1990—fiscal year 1990; is that correct?

Dr. KIRSCHSTEIN. That is correct.

Mr. CONTE. If you were to achieve an 8-percent budget increase, what priority areas would you invest in?

Dr. KIRSCHSTEIN. If we were to achieve an 8-percent increase over the fiscal year 1990 budget, we would need considerably increased funds. We would put that money into the basic investigator-initiated research grants in the fundamental areas that are of such excitement today: cell biology, genetics, structural biology, and pharmacological sciences.

The added funds would enable us to increase the number of research grants that we could pay to a more reasonable level, and achieve an award rate of probably about 29 percent when, for fiscal year 1990, our award rate is 23 percent.

PCR REACTION

Mr. CONTE. What is your Institute doing to take full advantage of PCR reaction?

Dr. KIRSCHSTEIN. Mr. Conte, the PCR reaction, which Dr. Fauci spent considerable time describing to you, is an enormously valuable tool for many studies, including basic studies in developmental biology. One can use very small fragments of genetic material, DNA, and amplify them through this technique, in order to learn a considerable amount about the molecular mechanisms involved in the development and growth of individual organisms. Furthermore, PCR is a very, very important tool in the diagnosis of many diseases which afflict mankind, including cancer and AIDS.

The diagnostic applications of PCR would be more important to the Institutes that have specific disease missions. However, the biotechnology industry, which NIGMS is attempting to encourage, is also finding the use of the PCR technique very important. The trainees we support are benefiting greatly from learning as much as they can about how to use the PCR techniques.

SCANNING TUNNELING MICROSCOPE

Mr. CONTE. The scanning-tunneling microscope is a major technological advance in biomedical research. Can you tell us what this special microscope does, and why is it so important?

Dr. KIRSCHSTEIN. This microscope, which was developed through support by NIGMS, is enabling basic scientists to, for example, visualize DNA, the genetic stuff of life, in a way that has not been possible before. We have known for years that DNA consists of two strands, which coil around each other. Scanning-tunneling microscopy can actually allow scientists to see those DNA coils, get a better feel for how they twist around each other, and determine which are the important points at which interactions between DNA and other molecules occur.

The microscope will be important for studying the growth and development of many organisms and may be very important in learning more about genetic defects and birth defects.

CELL CYCLE CONTROL

Mr. CONTE. Doctor, your budget documents mention the importance of basic research concerned with cell cycle control and cell-to-cell communications. Can you tell us in plain English what has been discovered and why it is so important?

Dr. KIRSCHSTEIN. Mr. Conte, each of us has millions of cells, which make up the tissues and organs of our bodies. Those cells, with rare exceptions, undergo cell growth and cell division.

If that growth is normal, and if the cell division is normal, then we continue to enjoy normal healthy function. If that growth and cell division goes awry, then sometimes cancer or other diseases arise.

Now, it has been a puzzle for many years how cell growth and division are controlled. One of many recent findings, and probably one of the very most important resulting from work by a cell biologist supported by the National Institute of General Medical Sciences, is the discovery of a factor called the maturation promotion factor. This factor controls cell growth, maturation, and division into two cells. We now know that this factor consists of two components. Further work will determine which component is found to contribute to normal growth and which to abnormal growth. This may prove extremely important in understanding cancer.

RIBOZYME AND CHEMZYME RESEARCH

Mr. CONTE. I am happy to hear that the scientists, who found RNA works as an enzyme, won the Nobel prize this year. What could be the future benefits of ribozyme research, and what about chemzymes? How do they work? What could be done with them?

Dr. KIRSCHSTEIN. The discovery that RNA can act as an enzyme was totally unexpected. That discovery has, in a very short period of time, become of enormous practical importance, because these RNA enzymes or ribozymes, can be tailor-made to cut ribonucleic acid or RNA at specific sites. One practical application is that, already, the National Institute of Allergy and Infectious Diseases, of which Dr. Fauci is the head, has put out a request for research grant applications to use these ribozymes to interfere with the progress of the AIDS virus infection. Since the AIDS virus is an RNA virus, the research that NIAID will support will determine whether ribozymes can be designed to cut the AIDS virus RNA in such a way as to inhibit its growth.

Now, chemzymes are a different set of chemicals. Chemzymes are artificially synthesized enzymes which can be tailor-made to facilitate certain important chemical reactions. An enzyme is a catalyst which increases the rapidity with which a chemical reaction occurs.

Dr. E.G. Corey from Harvard University, who has been working on chemzymes, has been able to synthesize tailor-made enzymes which can make specific reactions occur in such a way that they are what we call very stereo-specific. That means that the enzyme works primarily on part of a molecule which is active rather than on the other half of the molecule, the inactive portion. You may recall that in past years, I have ~~told you~~ and other members of this committee that chemicals consist of left-handed and right-handed molecules, one of which is active, the other, inactive. What the chemzyme can do is to fit selectively to the active molecule like a left-hand glove would fit to the left hand. This selectivity is very important because the chemical thus produced can do things more rapidly and efficiently, perhaps without toxic effects that might occur because of the presence of the non-active portion of the molecule. Therefore chemzymes will be very important in the development of new, effective, non-toxic, therapeutic drugs.

CELL BANK

Mr. CONTE. That is really something. I understand you are expanding the human mutant cell repository. What will this data base do? Which diseases currently under research might benefit from having this information, and how much are you requesting for the mutant cell bank?

Dr. KIRSCHSTEIN. Mr. Conte, we are expanding the human mutant cell repository, which has been in existence for a number of years. There are, in this cell bank, collections of cell samples representing a large number of diseases.

For example, all of the work which identified the fact that the Huntington's disease gene is located on chromosome 4, depended on deposits in the cell bank of numerous samples of cells in culture from patients with this disease.

Many other diseases are represented in the cell bank collections. Much of the work leading to the recent discovery of the gene for cystic fibrosis was done with cells coming from the cell bank. Very recently, the Retinitis Pigmentosa Foundation, a private organization dedicated to funding studies of blindness in individuals with a particular genetic defect of the retina of the eye, has been working with the people at our cell bank and with my staff to facilitate the cell bank's role in work on that disease.

Much of the work on muscular dystrophy was possible because of the cells deposited in that bank. Recently the cell bank began distributing DNA samples from special panels of cell lines. These should prove useful in gene mapping studies. Support for that cell bank, the human genetic mutant cell repository, in the fiscal year 1991 request, is $1,117,000.

Mr. CONTE. Thank you, Mr. Chairman.

Thank you, Dr. Kirschstein.

Mr. NATCHER. Mr. Stokes, I yield to you.

Mr. STOKES. Thank you, Mr. Chairman.

Dr. Kirschstein, it is always a pleasure and an honor to welcome you before our subcommittee and have the chance to ask you questions.

Dr. KIRSCHSTEIN. Thank you.

MINORITIES AND WOMEN IN SCIENCE

Mr. STOKES. I want to start by making reference to a book entitled, "Changing America: The New Face of Science and Engineering," which is a final report of a Task Force on Women, Minorities and the Disadvantaged.

In the report, with reference to blacks, it says this:

> "Blacks comprise only 2 percent of all employed scientists and engineers, even though they are 12 percent of the general population. They earn 5 percent of the baccalaureates and 1 percent of the Ph.D.s in science and engineering.
>
> "In 1988, only 47 United States blacks earned science Ph.D.s, only 15 earned Ph.D.s in engineering."

Under the title, Hispanics, it says:

> America's fastest growing minority group, Hispanics, comprise 9 percent of the population, only 2 percent of all employed scientists and engineers. They earn 3 percent of all bachelors degrees and 2 percent of all Ph.D.s in science and engineering.

The third section, entitled "White women," it says:

> White women comprise only 10 percent of all employed scientists and engineers, although they account for 43 percent of the U.S. population. In 1987, white women earned 22 percent of all bachelors degrees, and only 13 percent of the Ph.D.s in science and engineering. At the undergraduate level, they are twice as likely to be in the life sciences as in engineering. At the graduate level, they are eight times more likely to be in life sciences than in engineering.

In light of the fact that we are 10 years removed from the 21st century, and the white population in this country is shrinking at the same time the minority population is growing, it would seem to me that we face a crisis situation in terms of the United States being competitive in a global economy in the 21st century.

What are your views on that?

Dr. KIRSCHSTEIN. Mr. Stokes, I was honored to be chosen by the Department of Health and Human Services as its representative to the task force which you mentioned, the task force that prepared the report, "Changing America." I feel that it is one of the finest pieces of work with which I have been associated in my 35 years as a Federal civil servant. I quite agree both with all the comments that are in the report, and with your assessment that we are in what I would call a crisis situation.

That report also states that by the year 2000, 85 percent of the entering work force, whether it be laborers or white-collar, professional personnel, scientists or whatever, will be either women or minorities. The dearth of well-trained minorities entering all scientific areas, but biomedical science in particular, is very serious.

Because of that, the National Institutes of Health, as a whole, and the National Institute of General Medical Sciences, has, for many years, had specific programs aimed at improving the situation in regard to minorities. You well know that NIGMS has had the MARC, Minority Access to Research Careers program, since 1972.

The NIH, through its then-Division of Research Resources, has had the Minority Biomedical Research Support Program for a similar period of time. I was pleased that the MBRS, Minority Biomedical Research Support Program, was transferred, at the beginning of fiscal year 1990 to my Institute, because I think having both of those programs in NIGMS will allow closer coordination and cooperation, and will maximize the efforts that we are making to try to increase the number of minorities who are well-qualified and well-trained to enter biomedical research laboratories throughout this country.

I am also very pleased that the budget for the MARC program for fiscal year 1991 has been increased over that for 1990 by 25 percent, and the budget for the MBRS program increased by 8 percent. In addition, the Institute has become very active in one other effort which I believe you discussed with Dr. Raub on Monday. This effort is the award of supplements to regular research grants for minority investigators, graduate students, postdoctoral students or undergraduates. I am pleased that in fiscal year 1990, this Institute, NIGMS, will devote $2,000,000 to that minority supplements effort. We plan to increase our support to about $3,200,000 in 1991.

ATTRACTING YOUNG PEOPLE INTO SCIENCE

Mr. Stokes. You mentioned both MARC and the MBRS program. Over the years, you and I have worked together on those programs, and I think you have done an outstanding job under all circumstances, but particularly when dealing with severe budget constraints.

But don't we need to be doing something more before they even come to the stage where they are at MARC and MBRS, if we are really going to attack the problems that the report put out by your task force refers to? We have got to catch them early and interest them in the sciences.

I learned the other day at another hearing that only 6 to 7 percent of all the students throughout America—not just white or black, but all the students in America—are even qualified to enter college-level science courses. That is what Secretary Cavazos was referring to when he characterized America's school system as abysmal.

We have got to do something about trying to attract them long before they are eligible for MARC or MBRS.

Dr. Kirschstein. You are absolutely correct, Mr. Stokes. We are deeply concerned about the scientific literacy of our schoolchildren, at the elementary school level and the high school level, no less the college level. There is a diagram in that report called "Changing America," which shows that of the 400,000 high school sophomores who were enrolled in 1977, and who expressed an interest in entering careers in science, the number steadily decreases as they advance through high school and college, so that the number ends up being a pinpoint in size, a minuscule 9,400 who consider going to graduate school to obtain a doctorate degree in science; the number for the biomedical sciences clearly would be lower.

This is why I have been very interested in seeing what could be done by working with younger children. Many colleges, including, the historically black schools, and some of the schools that have large numbers of both Hispanic and black students that are supported by MBRS and MARC, sponsor what are called "Saturday schools" for our young children. These Saturday programs take children from the public schools, particularly minority children, and bring them to their laboratories to learn science on Saturdays.

There is such a Saturday school that has just started in the District of Columbia. It is being sponsored by the Carnegie Institution, and I am privileged to serve on the Board of Directors. It is called "First Light."

And, if I may, I would like to tell you about the first class of young children, from the inner city; of the District of Columbia. The majority of them were black youngsters between the 3rd and the 6th grade. At their first session, they went down to the Maine Avenue waterfront, and purchased squid. The teachers taught those children how to open up the squid and find the black ink sac and the quill. Then they gave each of the students a piece of paper and they wrote their names with the black ink from the squid's ink sac. Then the students took home that piece of paper, the ink sac, and the dissected squid and taught their parents all about it.

I met those children, and they were so excited they didn't know what to do. This is how we need to stimulate interest in science.

GOAL FOR MARC AND MBRS PROGRAMS

Mr. STOKES. That is a fascinating story. Now that you have both MARC and MBRS programs under your jurisdiction, what are some of your goals?

Dr. KIRSCHSTEIN. The overall goal is to increase both the numbers and the quality of the students who receive training in these programs. We can do this in a number of ways. We can maximize the opportunities with the new funds available, the 25-percent increase in the MARC program for fiscal year 1991. Instead of supporting 575 trainees as we did in 1990, we will be able to support 711. That is a substantial increase, and we are delighted with it.

In addition, out of the 98 institutions that are supported through the MBRS program, there are 46 which also have MARC programs. In those institutions, many of the MBRS students are not just juniors and seniors; some are freshmen and sophomores. You may remember that the MBRS students are considered student assistants to researchers, because the MBRS program mainly supports research.

What we would like to do is begin to look at the possibility, which we mentioned in a report prepared at your request, for moving the MARC honors undergraduate program into the first two years of college. We can take advantage of the experience of the MBRS program's involvement of freshmen and sophomores and enhance the activities of these students. We may have them work together in a program or a new set of programs. However, I think the goals of MARC and MBRS are separate, and we will not combine these programs. We will try to enhance them though, just as you and I want to do.

This will take some time, and I describe the plans of working with both programs in phases. In the short-range, nothing that was going on with the MBRS program, when it was part of the Division of Research Resources, will fall through the cracks. That would be disastrous. The short-range phase will be about a year, I would envision.

Then, in a medium-range plan, we will enhance the activities. Then gradually, with a group of advisors from the schools, we will do some long-range planning.

Mr. STOKES. Well, my time has expired. I just want to express my appreciation to you for your commitment, your achievements, and your sensitivity to the problems we have discussed here.

Dr. KIRSCHSTEIN. Thank you, Mr. Stokes.

Mr. STOKES. Thank you, Mr. Chairman.

Mr. NATCHER. Dr. Kirschstein, we want to thank you and your associates for appearing before our committee at this time on behalf of your budget request for the fiscal year 1991. It has been a good hearing, Dr. Kirschstein, just like it always is. We appreciate your appearing.

Dr. KIRSCHSTEIN. Thank you, Mr. Chairman.

Mr. NATCHER. The committee will now adjourn until 10:00 in the morning.

[Questions and answers for the record and the justifications follow:]

RESEARCH TRAINEE STIPENDS

Mr. Natcher. Your budget does not propose any research training stipend increases. Would it be better to budget for modest cost-of-living adjustments each year, rather than have a large increase once every few years?

Dr. Kirschstein. The NIH is primarily concerned about assuring the availability of adequate numbers of well-trained biomedical researchers in the United States, as we approach the 21st century, most particularly in light of demographic data that suggests the likelihood of significant shortages of scientific personnel by the year 2000. Within the dollars available, therefore, the NIH has given preference to maintaining support for the current level of trainees over providing inflationary increases for student stipends. In the ideal world, however, we would certainly agree that gradual year-to-year increases in stipend levels would be better than large abrupt increases, with no stipend changes in the intervening years.

NATIONAL BIOTECHNOLOGY POLICY BOARD

Mr. Natcher. Has the National Biotechnology Policy Board mandated by Congress begun its work?

Dr. Kirschstein. At present, administrative responsibility for the new National Biotechnology Policy Board rests with the NIH Office of Science Policy and Legislation. Secretary Sullivan signed the charter which formally established the Board in October 1989. However, it is our understanding that the process of selecting individuals for service on the Board has not yet been completed. When operational, the Board will consist of representatives from all of the Federal agencies that support or regulate biotechnology research, as well as representatives from the biotechnology industry, state biotechnology development programs, university research programs, and a charitable institution. It will also include a bioethicist.

TRAINING PERIOD FOR RESEARCH SCIENTISTS

Mr. Natcher. How many years will it be before a scientist who receives a traineeship in 1991 is ready to apply for research grants?

Dr. Kirschstein. Assuming he or she is in the first year of a predoctoral, or pre-Ph.D., training program, an individual receiving a traineeship in 1991 would not be ready to apply for a research grant until at least 1998. This assumes approximately five years of training to receive the doctoral degree in an area such as cellular and molecular biology, genetics, or the pharmacological sciences, and an additional two years of postdoctoral research training.

MINORITY PROGRAMS

Mr. Natcher. The new National Research Council study recommends that the Minority Access program be studied to test its relative efficacy. Do you plan to follow up on this recommendation?

Dr. Kirschstein. The NIGMS has just reorganized its Office of Program Analysis, and the new chief of that Office is currently planning evaluation studies of both the Institute's Minority Access to Research Careers, or MARC, and Medical Scientist Training programs, as recommended by the National Research Council, or NRC. The NRC indicated that it would like to see more up-to-date information than currently exists on the research careers of the individuals who have received support under these and other NIH training programs over the years, and we agree that such data should be collected and carefully analyzed.

Mr. Natcher. Do you have any long-run concerns that the NIH minority support programs focus almost exclusively on minority institutions, even though many minority students attend non-minority schools?

Dr. Kirschstein. Demographic trends point so emphatically to the Nation's need to attract more minorities into careers in biomedical science that it is imperative that the programs designed to do this reach minorities in many educational settings. This premise is shaping the efforts which NIH is taking to address the underrep-representation of minorities in biomedical research. The Minority Access to Research Careers (MARC) Program and the Minority Biomedical Research Support (MBRS) Program make a number of awards to institutions which have a predominant enrollment of minorities, defined as greater than 50 percent of the student population. However, these programs also award grants to institutions with a substantial, though less than 50 percent, enrollment of underrepresented minorities. In addition, the MARC program awards individual fellowships to graduate students and faculty members, most of whom pursue advanced studies at non-minority research intense schools.

Recently, NIH instituted a program to provide administrative supplements to research grants for the support of minority investigators, graduate students, and undergraduates. These awards are made to principal investigators of on-going research grants to add minority students, graduate research assistants, or investigators to the personnel supported to do laboratory research. The vast majority of such research experiences for minorities will take place at non-minority schools. In FY 1991, the institutes, centers, and divisions of NIH plan to devote $10.8 million to this program of research supplements for minority investigators.

Mr. Natcher. Despite NIH efforts, have we seen any measurable increase in the number of minority research scientists?

Dr. Kirschstein. The NIH programs to increase the number of minority biomedical research scientists have existed for less than 20 years, and have primarily supported college students who have gone on to higher education. These research training endeavors require about ten years before an individual scientist might be ready to try to establish an independent research career. Thus, it is not yet possible to expect that the NIH effort could result in a marked increase in minority scientists.

Nevertheless, the data and success stories coming from the various institutions having MARC and MBRS programs indicate that about 60 percent of the students are going on to higher education, aiming at graduate and professional degrees which are the prerequisites for launching a research career. Indeed, a number of MARC and MBRS graduates have earned doctoral degrees and are either engaged in postdoctoral research training or holding research positions in academia, government laboratories, or industry.

As noted above, NIGMS will be undertaking an evaluation of these programs which will collect and track data on the number of Ph.D. and M.D. graduates of these programs who are engaged in biomedical research.

Mr. Natcher. Does the Minority Access to Research Careers Program have any payback requirements?

Dr. Kirschstein. The same NRSA payback requirements that apply to other research trainees who receive support during their schooling under research training grants apply to the individual MARC predoctoral fellows and the Faculty Fellows supported under MARC funds. However, students receiving support through the Honors Undergraduate Research Training component of the MARC program do not incur payback obligations for that period of support, since the goal of the Program is to have these students obtain advanced degrees.

GRANT AWARD FUNDING GUIDELINES

Mr. Natcher. We understand that you have developed new grant award guidelines that would give preference to new investigators and limit increases for ongoing projects. Tell us more about these guidelines.

Dr. Kirschstein. The so-called guidelines to which you refer are a series of recommendations made to the Institute by the National Advisory General Medical Sciences Council at its January 1990 meeting in response to what the Council perceived to be a funding crisis in FY 1990. Council members felt that unfunded new and young investigators might become so discouraged that they might drop out of biomedical research--a situation which the members of the Council felt would be disastrous for progress in biomedical research and the economic well-being of the country. The Council articulated a set of principles to serve as guidelines for funding consideration as follows:

The mission of the National Institute of General Medical Sciences includes the support of basic research of the highest quality in the areas of biophysics and physiological sciences, cellular and molecular biology, genetics, and the pharmacological sciences. In addition, the Institute promotes the broadest possible diversity of ideas and approaches to these scientific areas, and encourages the ideas and talents of established investigators and of the young or new investigators who will provide the next generation of research accomplishments.

In order to achieve these goals, research grant applications recommended for approval by the National Advisory General Medical Sciences, NAGMS, Council are considered for funding using the following considerations:

- Scientific and technical merit of research, as determined by peer review;
- scientific program needs and balance;
- the availability of funds.

The NAGMS Council has recommended that, in times of extremely constrained funding, the Institute scientific staff take additional factors into account in making funding decisions:

a. In determining whether or not to make an award, Institute staff should give special consideration to a highly rated application from an applicant investigator who has no other significant source of research support.

b. Prior to considering awards to investigators whose total research support from all sources, including the pending award, exceeds $500,000 in direct costs, special analysis and justification should be required.

c. In determining the appropriate funding level for competing continuation awards, the Institute scientific staff will consider:

   - the previously committed level of support;
   - special needs for equipment;
   - whether the application is the first renewal after an initial award.

   Escalations in excess of ten percent over the previously committed level of support will require special justification.

The members of the National Advisory General Medical Sciences Council and the staff of NIGMS have no illusions that these limitations will not affect the momentum of some ongoing research project grants for which a competitive renewal grant application has been submitted. Indeed, it is quite clear that such restrictions could hinder an investigator's ability to carry out all the work proposed in his or her application. However, progress should still be sustainable at the previous level, and the Institute should be able to support a few more young and new outstanding investigators, who would otherwise not be able to conduct any research at all.

Mr. Natcher. When do you expect to put these guidelines into practice?

Dr. Kirschstein. Following the advice of the National Advisory General Medical Sciences Council, the Institute has already begun to put the guidelines into effect. The Council has requested that we report back to it on the initial impact of the guidelines, and we will do that at the Council's May 1990 meeting.

RESEARCH CENTER GRANTS

Mr. Natcher. How many of your nine research centers will be up for recompetition in 1991?

Dr. Kirschstein. Only one of the Institute's nine centers will be competing for support in 1991.

FUNDING SUPPORT FOR MBRS PROGRAM

Mr. Natcher. Show the total of support for 1990 and 1991 for the MBRS program from NIGMS and other NIH institutes.

Dr. Kirschstein. Estimated funding support for the Minority Biomedical Research Support Program is as follows:

Minority Biomedical Research Support Program
(Dollars in Thousands)

	FY 1990		FY 1991	
	No. Grants	Amount	No. Grants	Amount
NIGMS...........	98	$29,794	98	$32,326
NCI.............	--	2,582	--	2,801
NHLBI...........	--	2,418	--	2,624
NIDR............	--	161	--	175
NIDDK...........	--	1,462	--	1,586
NINDS...........	--	198	--	215
NIAID...........	--	693	--	806
NICHD...........	--	524	--	569
NEI.............	--	294	--	319
NIEHS...........	--	404	--	438
NIA.............	--	455	--	494
NIAMS...........	--	337	--	366
NIDCD...........	--	300	--	326
TOTAL NIH	98	$39,622	98	$43,045

PHYSICIAN RESEARCH TRAINEES

Mr. Natcher. What share of research trainees supported by NIH in 1989 were physicians? How does that compare to five and ten years ago?

Dr. Kirschstein. The NIH supported 11,225 trainees in FY 1989. Of these, 735, or 6.5 percent, were working toward the combined M.D.-Ph.D. degree in the NIGMS' Medical Scientist Training Program, while an estimated 2,569 or 22.9 percent already possessed the M.D. degree and were supported by a postdoctoral research training award.

Comparable data for 1980 and 1985 are as follows:

PHYSICIAN-RESEARCHER TRAINING
Number of Trainees

Program	FY 1980	FY 1985	Estimated FY 1989
M.D.-Ph.D. Training	665	683	735
Postdoctoral Training	2,030	2,402	2,569

In addition, the NIH supports a number of medical students engaged in short-term summer training experiences of 3 months or less.

GENETICS RESEARCH

Mr. Conte. Doctor, we have all heard about the tremendous opportunity awaiting us in the field of genetics research, especially in genetic transfer therapy. We ought to be more aggressive in pursuing all the major opportunities out there. Does your 1991 budget allow you to do this?

Dr. Kirschstein. The President's budget request provides approximately $214.9 million for the Institute's Genetics Program in FY 1991, an increase of $6.3 million over the $208.6 million available in FY 1990. This will enable us to support some, but certainly not all, of the excellent applications that are available in the basic genetic research area.

Mr. Conte. What are some of the opportunities we're missing out on?

Dr. Kirschstein. We will miss out on, or at least have to postpone, opportunities in several areas of research. First, we will not be able to fully fund studies on recombination in certain model organisms, such as yeast and bacteria, which frequently provide important background for studies on mammalian systems. Second, it is likely that we will not be able to fund projects designed to investigate, in more detail, how mammalian homologous recombination is affected by specific DNA sequences and by various treatments of the DNA. Third, we will be unable to fund research designed to reduce non-specific integration of foreign genes. Such studies would enhance our ability to develop safer and more efficient procedures for gene therapy.

Experts in the field believe that the promise of gene therapy is now greater than ever. Although successful gene therapy--the insertion of a normal gene into a patient's DNA to replace or supplement a defective gene--has yet to be accomplished in humans, the necessary foundation is gradually being constructed. For example, scientists are now able to use one of several strategies to introduce functional genes into cells in culture. In studies using mice, it is now possible to show that, under certain circumstances, the genes that are inserted are expressed in the proper tissues. Several technical obstacles still remain, however, before gene therapy can become feasible. The first is that the efficiency of introducing foreign genes is still lower than is desirable. Second, even when genes are inserted into the cell's DNA, they often do not lead to the expression of enough normal protein to be therapeutically effective. Finally, when normal genes are introduced into cells, there is a chance that they will disrupt the function of other genes.

Despite these technical difficulties, scientists active in the field of gene therapy research are optimistic about the prospects of eventual success. Furthermore, as an increasing number of disease-causing genes are identified and isolated, the potential for the development of gene therapy technology keeps growing.

Over the last 15-20 years, basic studies on genetic mechanisms and recombinant DNA technology, supported by NIGMS, have laid the groundwork for all the current experiments on gene therapy. More recently, NIGMS grantees have made remarkable progress in one promising approach to gene therapy, an approach based on homologous recombination--a process that occurs normally in cells at the time of division. Homologous recombination results in the exchange of pieces of DNA between two chromosomes. First demonstrated in yeast and other lower organisms, scientists have now found that a "foreign" gene can also be made to replace a gene with a similar sequence when introduced into mammalian cells in culture. When considered as a means of gene therapy, homologous recombination has the advantage over alternative strategies in that the foreign gene inserts in a highly specific manner, reducing the risk that other, normal genes might be disrupted.

Basic studies on mechanisms related to gene therapy, especially homologous recombination, remain an important research area for NIGMS. To promote scientific collaboration between investigators doing basic research and those carrying out more applied studies, NIGMS co-sponsored a workshop with NIDDK and NICHD in November 1989, entitled "Application of Homologous Recombination to Human Disease." Participants discussed both their continuing basic studies, supported mainly by NIGMS, and the application of gene therapy to neurological diseases, lysosomal storage diseases and diseases of the blood and muscle, supported mainly by the categorical Institutes.

GENBANK

Mr. Conte. Your Institute sponsors the GenBank program, which is the central information center for nucleotide sequence data.

How has the bank facilitated genetic research since it was started 8 years ago?

Dr. Kirschstein. GenBank has proved an essential tool for molecular biologists. The determination of the amino acid sequence of a protein by first determining the nucleic acid sequence has become the method of choice. The data in GenBank allows scientists to quickly determine this amino acid sequence, once the nucleic acid sequence has been found through a simple search of GenBank. Once the protein sequence has been determined, information about the folded structure of the protein can be inferred. It is a goal of other research funded by this Institute to be able to predict the structure from the sequence and, in turn, relate this to the function of the protein. In addition, a comparison of the structure of a newly discovered gene/protein sequence with those already in the database often yields important discoveries. One well-known case is the discovery of the similarity between epidermal growth factor, essential to the orderly growth and division of the cells of the skin, and the protein coded by an oncogene, a normal gene which can go awry and cause cancer.

Mr. Conte. Is the bank working with the new Human Genome research center, and is the bank contributing to the center's projects?

Dr. Kirschstein. The GenBank project officers and GenBank staff are working closely with the staff of the National Center for

Human Genome Research to ensure coordination with respect to common objectives. It is expected that, when data from large scale genetic sequencing projects become available, they will be made available through GenBank. To this end, the database at GenBank has been designed to accommodate the needs of such large scale genetic sequencing efforts.

In addition, GenBank collaborates closely with sister efforts in Europe and Japan. This collaboration will ensure that the results of nucleic acid sequencing in Europe, where the entire genetic sequence of chromosome 3 in yeast has been determined, and in Japan, where the entire nucleic acid sequence of the E. coli gene was worked out, will be made available rapidly to researchers throughout the world.

DIAGNOSTIC IMAGING

Mr. Conte. What is your biophysics section doing to improve diagnostic imaging techniques?

Dr. Kirschstein. Research on diagnostic imaging techniques is primarily supported by the National Cancer Institute. Although the NIGMS, at one time, had responsibility for some of this research, the Institute transferred all of its grants in this area to the NCI some years ago. However, the fundamental research through which such diagnostic imaging techniques were developed, was supported by NIGMS.

RESEARCH PAYOFFS

Mr. Conte. Can you give us a few examples of how our investment in your Institute's research programs have been good ones for the country?

Dr. Kirschstein. The basic research supported by the NIGMS has led to the development of the American biotechnology industry, the Human Genome Project and one of the most effective drugs ever used in cancer treatment, cis-platinum. More recently, such research has led to the development of "chemzymes," artificial enzymes that are starting to have a major impact on the pharmaceutical and chemical industries because they allow chemists much greater control over the products of their chemical reactions. Research supported by NIGMS has also led to the development of "ribozymes," RNA enyzmes that are considered to hold enormous potential as weapons in the war against AIDS and other serious viral infections.

RECEPTOR RESEARCH

Mr. Conte. I hear that your Institute is involved with receptor research. Can you tell us how better knowledge of cell receptors is beneficial?

Dr. Kirschstein. A better knowledge of cell receptors is vital to understanding how cells work in a healthy body, and how a wide range of diseases can occur when they do not. Cell receptors are proteins that are normally located on the outer surface of cell membranes. One of their primary roles is to serve as "docking sites," to which hormones and other signal-carrying molecules attach before transmitting their messages to the interior of the cell--messages such as "Manufacture more proteins!"

Dr. Alfred Gilman, an NIGMS grantee at the University of Texas Southwestern Medical Center, won the prestigious Lasker Award in 1989 for his discovery of the role of receptor-associated G-proteins in communication between cells. Flaws in G-protein function have already been shown to play a role in such serious diseases as cholera and whooping cough, and in one form of mental retardation.

One of the most recent illustrations of the payoff of receptor research relates to followup studies associated with the 1987 success of Dr. Ronald Evans, an NIGMS grantee, in isolating a cell receptor for a vitamin A derivative, called retinoic acid, the active ingredient in Retin-A cream. Dr. Evans showed that the retinoic acid receptor is essential in the translation of the message carried by the retinoic acid itself into a signal telling the cell to carry out certain developmental functions. A series of articles which have recently appeared in various scientific journals now strongly suggest that retinoic acid is a "master regulator" in developmental biology. It plays a vital role in determining the shape of the brain, the spinal cord, the face, the limbs, the heart, and the bony skeleton, as well as the specialized patterns of these organs. Experts believe that further research in this area could provide physicians with a better understanding of why the development of certain cells and organs goes awry, causing birth defects, tumors, and other problems.

PLAN TO ASSIST NEW INVESTIGATORS

Mr. Conte. A news report said that you are giving new investigators a higher priority for grant funding, under guidelines developed by your Advisory Council.

Can you tell us more about the recommendations of the Council?

Dr. Kirschstein. The NAGMS Council recommended the following to the Institute at the Council's January 1990 meeting. These guidelines are designed to get the most mileage possible out of available funds, while also looking to the future by providing some assistance to young investigators:

a. In determining whether or not to make an award, Institute staff should give special consideration to a highly rated application from an applicant investigator who has no other significant source of research support.

b. Prior to considering awards to investigators whose total research support from all sources, including the pending award, exceeds $500,000, direct costs, special analysis and justification shoul~~d be requ~~ired.

c. In determining the appropriate funding level for competing continuation awards, the Institute scientific staff will consider:

- the previously committed level of support;
- special needs for equipment;
- whether the application is the first renewal after an initial award.

Escalations in excess of ten percent over the previously committed level of support will require special justification.

Mr. Conte. How are you implementing these guidelines?

Dr. Kirschstein. The guidelines are being used in accordance with the Council's wish that they be be taken into consideration, along with other factors, when funding decisions are made. They will only affect a limited number of applications each year. The staff will report back to the Council on the initial impact of these guidelines at the Council's May 1990 meeting.

BIOTECHNOLOGY

Mr. Conte. Doctor, biotechnology is critical to American industrial competitiveness in the future decades. Your Institute is recognized as a world leader in biotechnology research.

Can you bring us up to date on what your Institute is doing in biotechnology?

Dr. Kirschstein. The NIGMS supports over $440 million per year in basic research activities related in some way to biotechnology, most particularly through the Institute's Genetics Program. Beyond this, the Institute supports a biotechnology research training initiative, which is designed to provide some of the highly trained manpower needed by America's rapidly growing biotechnology industry, which now employs over 53,000 people. Two years ago, NIGMS started this biotechnology research training program to prepare scientists to become highly qualified, not only to do basic research, but also to apply such research in the development of commercial products by the biotechnology industry. The NIGMS biotechnology research training grants are designed to have trainees spend time in laboratories, both in universitites and biotechnology companies. The President's budget request provides approximately $4.3 million for the support of 190 biotechnology trainees in FY 1991.

RESEARCH TRAINING

Mr. Conte. Our Committee has heard a number of dire predictions regarding the critical shortages of scientists and engineers in the coming years.

What is your Institute doing to help head off this crisis?

Dr. Kirschstein. The NIGMS is the primary source of support for research training at NIH, funding about two-thirds of the predoctoral, or pre-Ph.D., trainees who receive NIH assistance. The

Institute's budget request would provide support for 4,006 research trainees in FY 1991, at a cost of $85.6 million. Most of these trainees would be at the predoctoral level.

Mr. Conte. In your professional judgment, how much should your Institute be spending for research training in FY 1991?

Dr. Kirschstein. In my best professional judgment, I feel $111 million could be effectively used in FY 1991 to support approximately 4,962 trainees under NIGMS programs. In my opinion, this would more appropriately address the need to train replacements for aging scientists, and better deal with the increasing personnel demands of a biotechnology industry growing at rate of almost 30 percent per year.

IMPORTANCE OF BASIC RESEARCH

Mr. Conte. The President's budget request said that: "Basic research is the wellspring of fundamental knowledge that can eventually lead to new products and new processes. Support for basic research is an essential investment in the Nation's scientific and technological future."

Doctor, do you agree with the President's characterization of basic research?

Dr. Kirschstein. I absolutely agree. The basic research supported by the NIGMS, for example, resulted in the development of the recombinant DNA techniques that later led to the development of the American biotechnology industry. The scientific, technical, and economic future of the Nation now rests, in no small measure, on the success of this industry in developing pharmaceuticals, chemicals, plants, and foodstuffs of commercial value.

SUPPORT FOR RESEARCH TRAINING

Mr. Stokes. How much did you originally request for research training in 1991?

Dr. Kirschstein. NIGMS originally requested $115.1 million for research training in FY 1991.

Mr. Stokes. How many trainees would your original request support, as compared to your current budget request?

Dr. Kirschstein. The original request would have supported 4,614 trainees, compared to the 4,006 trainees to be supported under the President's FY 1991 budget request.

MBRS PROGRAM

Mr. Stokes. This fiscal year, NIGMS has taken over administrative responsibility for the MBRS Program. Since you also have responsibility for the MARC Program, this makes your Institute the lead Institute at NIH with regard to minority-targeted programs.

How does the FY 1991 request for this Program compare with the FY 1990 level? In your professional judgment, is this level of support adequate?

Dr. Kirschstein. The NIGMS FY 1991 budget request for the MBRS Program is $32.3 million, an eight percent increase over the comparable FY 1990 level of $29.8 million. The $10.7 million for the MBRS Program in the budget requests of the other institutes at NIH also represent an eight percent increase over their FY 1990 contributions to the program. I am pleased with these increases.

MARC PROGRAM

Mr. Stokes. How many trainees can be supported under your budget request for the MARC Program? How does this compare with 1989 and 1990?

Dr. Kirschstein. The FY 1991 request for the MARC Program will support an estimated 711 trainees. This represents a significant increase above the 575 trainees to be supported in FY 1990, and the 479 trainees supported in FY 1989.

Mr. Stokes. Given the projected shortage of American scientists in the coming years, and the related need to attract minorities into biomedical research careers, is this an adequate level of support?

Dr. Kirschstein. The FY 1991 budget request will permit a sizable expansion of the MARC Program's activities, including a pilot effort to extend eligibility for support under the Honors Undergraduate Research Training Program to honors students in their freshmen and sophomore years. Along with the other minority-targeted programs at NIH, which are also experiencing significant growth, this level of support for the MARC Program will allow us to make important strides toward the goal of increasing the numbers of minorities engaged in biomedical research.

GENETICS RESEARCH

Mr. Stokes. Your Institute's Genetics Program is the largest single source of federal support for basic research in genetics. This year, two of the grantees of this Program were jointly awarded the Nobel prize in chemistry, as noted in your opening statement. What other important advances are coming out of this Program? And, how close are we to effective methods of diagnosis, treatment, and prevention of genetic diseases?

Dr. Kirschstein. Effective methods of diagnosis, based on recombinant DNA technology, are already available for a large number of genetic disorders. In some cases, diagnosis is based on the close association of the disease-related gene to a known marker, as in Huntington disease and adult polycystic kidney disease, or by analysis of the actual disease gene, as in thalassemia and phenylketonuria. Scientists are optimistic that it will soon be possible to devise an accurate test to screen the population for cystic fibrosis (CF). Such a test would be the direct outcome of progress described below in the identification of the gene which is defective in CF. Progress is also being made on the treatment of genetic diseases using gene therapy. Although such an approach is not yet feasible in humans, research described below is bringing us closer to the day when it will be the treatment of choice for certain genetic disorders. Furthermore, as specific disease-causing genes are identified, and as their role in the etiology of hereditary diseases is determined, it should be possible to design more rational therapies to treat the symptoms of the disease.

Significant new advances being developed by NIGMS grantees include the following:

- Multi-Factorial Disorders: In a number of common disorders, such as heart disease and certain forms of cancer, genetic and environmental factors appear to play roles in the development of illness. There is currently great interest in understanding such complex disorders. As more progress is made in defining the genetic and environmental components involved, individuals at-risk can be alerted to modify their lifestyles to reduce their chances of being affected. Toward this goal, the NIGMS Genetics Program has supported, for the past eight years, a series of Gene Analysis Workshops, in which epidemiologists, population geneticists, and medical geneticists have collaborated internationally to develop models to help explain the etiology of complex genetic disorders, such as breast cancer, diabetes, multiple sclerosis, affective disorders, and celiac disease.

- Expansion of the Knowledge Base: Advances in technology and the resulting expansion in our knowledge base have made this a time of unprecedented productivity and promise in the fields of genetics and molecular biology. Basic science, funded in part through the Genetics Program, has contributed greatly to laying the groundwork for exciting advances in many areas of medicine. In some cases, the translation of advances in basic genetics into the diagnosis, treatment, or prevention of genetic diseases is rapid and direct. More often, however, medical advances build on a foundation of basic knowledge involving diverse contributions over long periods of time. Furthermore, it is a characteristic of this process that it is difficult to predict in advance which areas of basic research are likely to prove most important in subsequent medical advances, with exciting advances often coming from unexpected directions.

° Use of DNA Analysis in Disease Diagnosis: An area of especially rapid progress is the use of DNA analysis for the diagnosis of genetic diseases. A broad array of genetic and molecular tools has made possible the identification of DNA sequences responsible for particular genetic diseases. Work funded initially by the Genetics Program, and later by the categorical institutes, by private foundations, and by industry, has provided the technology whereby disease-causing genes can be identified and diagnostic tests developed indicating their presence. Recently, the gene responsible for CF was identified by several groups, including Dr. Francis Collins of the University of Michigan and his coworkers. This important advance was made possible by Dr. Collins' work, supported by NIGMS, in which he developed a technique called "chromosome jumping." The precise defect responsible for the majority of cases of CF has also been pinpointed and has been shown to be a deletion of three nucleotide units from the gene.

° Screening Techniques: The work of another NIGMS grantee, Dr. Jack Griffith of the University of North Carolina, has led unexpectedly to a simple and inexpensive screening method to identify a majority of all couples at risk of producing a child with CF. This method is based on Dr. Griffith's observation that deleting a small segment of one strand of a DNA molecule produces a kink that can be detected easily. While the work that produced this observation was in no way related to CF, it has been translated with unusual speed, into a practical application related to improving the diagnostic test for this very common hereditary disease.

° Gene Therapy: Increasingly rapid progress is being made in the development of techniques for replacing defective genes with normal counterparts to correct some hereditary diseases. While gene therapy is not yet practical for humans, successful experiments have been performed in mice. Important progress is being made by NIGMS grantees in understanding homologous recombination, the basis for the most attractive strategy for gene replacement, and in designing DNA "vectors" for introducing normal gene sequences into cells. Studies of homologous recombination promise to improve the precision with which genes can be targeted to the exact location on the chromosome where they can correct a disease gene without accidentally causing any additional DNA defects.

° Therapeutic Drug Development: Work by NIGMS grantees on enzymes that act on DNA has continued to produce medical applications. Basic work by NIGMS grantees Dr. James Wang of Harvard University and Dr. Leroy Liu of Johns Hopkins University on DNA topoisomerases, enzymes that twist DNA, has led to a new class of anti-tumor drugs. The development of such drugs is continuing in both of their laboratories as well as elsewhere. Similarly, the work of NIGMS grantee Dr. Melvin Simpson of the State University of New York at Stony Brook has suggested that a group of new drugs might be important for, and now are being tested for use against AIDS. Dr. Simpson noted that the anti-AIDS drug, AZT, affects one of the DNA synthesizing enzymes of the cell and he proposed that this action might be responsible for some of the toxic effects of AZT. By looking for analogs of AZT that do not affect this DNA enzyme, Dr. Simpson was able to find several compounds that may prove superior to AZT for the treatment of AIDS.

° Knowledge of Chromosome Structure: Genetic diseases, including cancer, can be caused by errors in the organization and sorting of chromosomes during development. Advances now being made in the understanding of chromosome structure and organization promise to improve our understanding of how such errors occur. Exciting work by an NIGMS grantee, Dr. Elizabeth Blackburn of the University of California at Berkeley, is casting new light on the mechanism by which the ends of chromosomes, which are particularly prone to abnormalities, are protected by specialized structures called the telomeres. Dr. Blackburn has found that telomeres are attached to the ends of chromosomes by a unique enzyme called telomerase, which uses RNA as a template to attach to a single strand of DNA. This strand appears to fold into a form that both identifies the end of the chromosome and prevents it from attaching to other chromosomes.

° Problems of Gene Expression and Regulation: Rapid progress is also being made in broad areas related to gene expression and its regulation. New insights are being provided into the regulation of RNA synthesis, RNA splicing, and protein synthesis, insights that are for the most part not directly translatable into medical advances, but are ultimately of clear relevance to the understanding and control of genetic diseases. Occasionally the connection is more direct and apparent. For example, NIGMS grantee Dr. Ronald Evans of the Salk Institute, La Jolla, CA, has been studying a gene called c-erbA. A slightly altered form of this gene can cause cancer. Dr. Evans found that c-erbA encodes a thyroid hormone receptor protein which binds to DNA and regulates the expression of several other genes in response to the hormone. The cancer-causing form of the gene binds to DNA, but has lost the ability to respond to the hormone. This work establishes a connection between the regulation of gene expression and cancer, and promises to help to explain the causes of cancer.

RATIONAL DRUG DESIGN

Mr. Stokes. Dr. Kirschstein, there have been numerous articles written in the lay press about "rational drug design"--something also noted in your justification materials. What is rational drug design and why is it important?

Dr. Kirschstein. For centuries, drugs have been discovered by a process of trial and error. Most drugs available today were discovered by means of large drug screens of thousands of compounds in a variety of systems, looking for various types of biological activity. New technologies are now available, however, which will enable scientists to first identify the molecule to which they want the drug to bind, then to determine the exact structure of that molecule, and knowing that structure, to build a drug which will exactly fit that molecule. One obvious benefit of this strategy is the elimination of a host of undesirable side effects which frequently result because a drug not only acts on the molecule of choice but also on other similar ones. Thus, rational drug design is the approach to designing drugs based on a knowledge of the structure and function not only of the target molecule, but often of only the active portion of the target molecule. This will ultimately provide safer and more effective drugs, and, in the long run, save millions of dollars related to the unnecessary screening of chemicals in a search for therapeutic effects.

GRANT AWARD SUPPLEMENTS FOR MINORITY INVESTIGATORS

Mr. Stokes. Last April, NIH announced a new "Initiative for Underrepresented Minorities in Biomedical Research." Under this initiative, current recipients of NIH grants can receive additional funds for attracting and encouraging minority scientists and students to assist in their research.

How much has NIGMS allocated for the support of this effort?

Dr. Kirschstein. The NIGMS has allocated approximately $2 million for the support of this effort in FY 1990, and approximately $3.1 million in FY 1991.

Mr. Stokes. What has been the response of the scientific community to this initiative?

Dr. Kirschstein. The NIGMS funded 14 awards under this program in FY 1989, and expects to fund an additional 50 awards in FY 1990. To date, the Institute has received 58 applications for awards under the program this year. This reflects a reasonably good response to this new program.

SUPPORT FOR GENETICS RESEARCH

Mr. Early. Dr. Kirschstein, according to a recent article in the Washington Post, the Nation's rapidly rising health care costs are likely to reach $661 billion in 1990, about 12 percent of the Gross National Product. It is my understanding that as much as 20 percent of these costs, or $132 billion this year alone, are associated with inherited disorders.

With this in mind, how much is provided in your 1991 budget request for basic research in genetics? And, how does this compare with recent years?

Dr. Kirschstein. The President's budget request provides approximately $214.9 million for the Institute's Genetics Program in FY 1991. With the exception of $13.9 million allocated to research training, virtually all of these funds will be used for the support of basic research in genetics.

The Genetics Program budget was $209.5 million in FY 1989, and is $208.6 million in FY 1990. Approximately $14 million was allocated for research training in each of these years, with the remainder allocated to basic research.

GENETICS RESEARCH PAYOFFS

Mr. Early. Could you give us an example or two of some of the research being supported by your Genetics Program that you feel will lead to important payoffs in the coming year?

Dr. Kirschstein. By its very nature, basic research often pays off in unexpected ways. For example, NIGMS supports research on enzymes that affect the way DNA is wound and unwound as the cell undergoes division, or as the expression of particular genes is turned on and off. This unwinding and rewinding is carried out by a set of enzymes called topoisomerases. Several years ago, in the course of basic studies on the mechanism of action of topoisomerases, a Genetics Program grantee, Dr. Leroy Liu of Johns Hopkins University observed that certain drugs, known to be effective against the growth of cancerous tumors, interfered with the action of the enzymes he was studying. As a result of further investigations, Dr. Liu proposed that interference with topoisomerases accounted for these drugs killing tumor cells. Based on this insight, Dr. Liu and another Genetics Program grantee, Dr. James Wang of Harvard University, are now investigating, with support from the National Cancer Institute, other compounds that interfere with topoisomerases. These studies have led to the identification of some promising new anticancer drugs.

The Genetics Program also actively supports studies related to gene expression and the many mechanisms by which gene expression is regulated. These studies have led to a steady stream of new insights into how cells function normally. Although the results of these studies do not necessarily translate immediately into medical advances, they provide the foundation for understanding the underlying causes of disease. One outstanding example of this is the research of Dr. Ronald Evans of the Salk Institute in La Jolla, CA. He has demonstrated that a gene called c-erbA codes for a specific receptor protein which binds to DNA and regulates the expression of several other genes in response to thyroid hormone. What makes his finding particularly interesting is the fact this receptor acts to turn on other genes, while a slightly altered form of the c-erbA gene is an oncogene which causes a cell to become cancerous because it prevents the other genes from being "turned on," even when thyroid hormone is present. His discovery, that preventing a gene from turning on can also lead to cancer, is forcing oncologists to reformulate their thinking about the mechanisms by which cancers are induced, and promises to open new avenues of investigation into cancer treatment.

Dr. Evans' findings result from a broader investigation underway in his laboratory that has helped to define a "superfamily" of hormone receptors that are involved in gene regulation. In addition to the thyroid hormone receptor, this superfamily includes receptors for the sex hormones, for adrenal hormones, and surprisingly, for vitamins A and D. These hormone receptors all are able to "turn on" genes only after each of them has interacted with a specific hormone molecule. For example, a number of reports have demonstrated the importance of retinoic acid--a form of vitamin A best known for preventing age-related wrinkles--in normal fetal development.
Dr. Evans' studies are improving our understanding of how vitamin A derivatives act as critical regulators of normal fetal development and might provide insight into the causes of certain congenital or developmental defects.

Mr. Early. Support for research in genetics seems to be a good investment. Discoveries made by NIGMS grantees have already led to the development of recombinant DNA techniques, the biotechnology industry, and the human genome project. Where is this program going to take us in the future?

Dr. Kirschstein. Research supported by the Genetics Program will continue to have an impact on the evolving biotechnology industry. New approaches, such as the use of "designer ribozymes," are likely to be used to develop treatments for viral infections, including AIDS. Ribozymes, or RNA enzymes, were originally discovered by NIGMS grantees Thomas Cech of the University of Colorado and Sidney Altman of Yale University. Their discovery, for which they were awarded the Nobel Prize in Chemistry in 1989, provided the basis for attempts to construct ribozymes which would specifically cleave, and thereby inactivate, other pieces of RNA, such as the RNA molecules in infectious viruses. Just last week, an investigator at the National Cancer Institute, in collaboration with investigators in several institutions in California, reported in Science that they were able to engineer ribozymes that reduce the levels of HIV-1, the virus which causes AIDS, in human cells in culture. This holds great promise for developing a treatment for AIDS. A similar approach could be taken in the treatment of other viral diseases. Ribozymes also could have widespread applications in agriculture, since they might be engineered into plants so as to protect against diseases that could destroy important crops.

Research supported by the Genetics Program is also providing a strong foundation for future gene therapy to correct hereditary disorders. Investigators have been studying the process of homologous recombination, first in yeast and bacteria, and more recently in mammalian cells. Homologous recombination occurs during the division of cells and results in the exchange of genes between chromosomes. Studies of homologous recombination have led to the development of an approach whereby potentially therapeutic genes can be targeted to integrate into a particular chromosomal location. Introducing such genes into a cell's DNA by homologous recombination is much more specific than are other modes of introducing "foreign" genes, and thus reduces the possibility that these genes will disrupt the expression of a gene essential to the survival of the cell. Since gene therapy is likely to be an important treatment for a number of genetic disorders, the support that NIGMS currently provides for research on homologous recombination is another good investment.

STRUCTURAL BIOLOGY RESEARCH

Mr. Early. The National Academy of Sciences recently issued a report entitled Opportunities in Biology. One of the areas highlighted in this report is "Structural Biology"--one of the fields mentioned in your justification materials. Doctor, please tell us why both you and the Academy consider this area important. And, tell us what your Institute is doing in this area.

Dr. Kirschstein. Structural Biology is a relatively new area of science concerned with understanding the detailed molecular structure of molecules having biological importance. In particular, this involves macromolecules such as proteins and DNA. The importance of this area is that an understanding of structure can lead to a knowledge of how these molecules operate and how they interact with other important materials such as drugs. Not only is this critical for dealing with problems of disease, but, combined with molecular genetics, can lead to the development of new products by the biotechnology industry.

Most of the NIGMS support for structural biology is provided through the Biophysics and Physiological Sciences Program. This includes approximately 500 research grants totalling roughly $72 million/year. Beyond this, however, the Institute provides support for both research and research training activities in the structural biology area that are specifically focused on AIDS.

The Institute's AIDS-related research program, budgeted at a level of $9.5 million in FY 1991, is concerned with the development of detailed information on the three-dimensional structure of AIDS-related proteins, as part of an effort to design effective new antiviral agents. The AIDS-related research training program was developed in response to a 1986 National Academy of Sciences report, which called for the training of more researchers in the field of structural biology, highlighted by the Academy as an area of high priority in the war against AIDS. The Institute's budget request provides approximately $5.6 million for the support of 242 AIDS-related structural biology trainees in FY 1991.

CELLULAR AND MOLECULAR BASIS OF DISEASE PROGRAM

Mr. Early. The NIGMS supports the most basic research funded by the NIH. This includes the kind of research funded by the NIGMS cell biology program. Why is it important to invest in this program?

Dr. Kirschstein. Cell biology is emerging as one of the "hottest" areas in modern biomedical research. All living organisms are cells, or are composed of cells. Because they are surrounded by membranes with limited permeability, cells can often be cultured and maintain their viability, if kept in an appropriate medium. This makes them ideal for addressing many basic biological questions that are rooted in the cell, or in an intracellular component. As the field of biomedical science has exploded, we have also seen a merger, and a commonality of approach, among its previously more isolated branches. Thus, we now have cellular neurobiology and cellular immunology, in which neural and immune cells are used for basic investigations relevant to all cell biology. The findings about basic cell biology can then be applied to specific cell types and human diseases. Pathologists use our understanding of cell structure, chemistry, and growth to diagnose diseases and disorders. Pharmacologists and pharmaceutic chemists design drugs based on an understanding of cell physiology and biochemistry. The list could go on, but the essential point is that cell biology is one of the central disciplines in biomedical research.

Mr. Early. Could you give us an example of an important discovery that has come out of the program and how it has impacted on the health care of the Nation?

Dr. Kirschstein. Over the past decade or more, the Cellular and Molecular Basis of Disease Program has supported research into the structure and function of ion channels. These channels are structures in the membranes of cells which allow, temporarily or permanently, specific types of ions to cross the membranes. Researchers have been able to describe a variety of naturally occurring channels, as well as synthesize new ones, or modify native channels. Some channels have been shown to be very specific for metal ions, such as potassium or calcium. Investigators have also explored some specific blockers of individual channel types. Most interesting are some of the agents found to block calcium channels in many tissues. Investigations by physiologists, pharmacologists, and cardiologists have developed therapeutic agents called calcium channel blockers. These compounds reduce calcium entry into the heart, thus controlling arrhythmias. Another class of artificial or semi-synthetic channels which are permeable to many cations are certain antibiotics. Understanding the basic mechanism of ion permeability of these antibiotics, such as gramicidin, has provided important information for designing new ones. Lastly, a naturally occurring family of channel-forming compounds from bacteria, called BT, are used as specific, selective, and environmentally safe insecticides. These are common insecticides against beetles and moths.

Mr. Early. Give us an example of a recent discovery coming out of this program that is likely to lead to better treatments or cures.

Dr. Kirschstein. Recently, NIGMS-supported scientists have discovered two key proteins, maturation promoting factor and cyclin, involved in regulating the cell cycle. Their presence is necessary, for cells to reproduce and develop, and changes in their concentration cause transition from one cell cycle stage into the next. The system is turning out to be quite complex, the more we look at it. However, for the first time in half a century, we have a major opportunity to explore the control of cell division and reproduction. One of the questions being asked is how other agents known to modulate cell division affect these essential components. For example, the products of oncogenes have been shown to interact directly or indirectly with the recently discovered cell cycle proteins. This suggests that transformation of normal cells into cancerous ones occurs through modulation of the cells' normal machinery for controlling cell division. We now can hope to understand why cancerous cells proliferate. Control of that proliferation may be possible with our expanding knowledge of the basic cell cycle.

SUPPORT FOR RESEARCH PROJECT GRANTS

Mr. Early. Doctor, almost 80 percent of your 1991 budget request is for the support of research project grants. Why do you put so much emphasis on this support mechanism?

Dr. Kirschstein. NIGMS emphasizes the investigator-initiated research project grant because of its suitability in advancing the mission of the Institute. Basic research studies flow from the creative ideas of individual scientists who want to pursue hypotheses about the fundamental structures, functions, and processes of genes, cells, biologically active molecules, and organic systems. Invariably the discoveries made in pursuing the facts related to these hypotheses raise further questions that, in turn, give rise to more intriguing avenues of study. The research project grant mechanism permits basic scientists to pursue their hypotheses toward whatever end the laboratory work carries them, giving them both the freedom and the personal incentive that foster significant accomplishment.

Mr. Early. How many new and competing grants will NIGMS be able to support under the FY 1991 budget request, and how does this compare to the number funded in FY 1990 and FY 1989?

Dr. Kirschstein. A total of 819 new and competing grants would be funded under the FY 1991 budget request. In FY 1990, an estimated 637 new and competing grants will be funded, while in FY 1989, 788 were awarded.

Mr. Early. What percentage of approved grants would be funded and how does this compare to the previous two years, and with the traditional level of support in the past?

Dr. Kirschstein. The percentage of approved grants to be funded, or the award rate, for FY 1991 is projected to be 26 percent, compared to 23 percent in FY 1990 and 29 percent in FY 1989. In the years prior to FY 1989, the award rate ranged from 36 percent to 45 percent.

Mr. Early. How many new and competing research project grants did you propose in your original FY 1991 request to NIH?

Dr. Kirschstein. NIGMS originally proposed to support 1,277 new and competing research project grants in FY 1991.

Mr. Early. To what payline percentile and/or award rate would we have to fund to satisfactorily support all of the important research opportunities worthy of being explored?

Dr. Kirschstein. An award rate of about 45 to 50 percent would permit NIGMS to support most of the promising research opportunities which the peer review process deems worthy of being pursued. This award rate equates to a 41st to 46th percentile payline.

Mr. Early. How much extra money would this require?

Dr. Kirschstein. At the same level of downward negotiations assumed in the FY 1991 budget, an additional $93.1 million would be necessary to achieve a 45 percent award rate. Additional funds would be required to return to historical levels of negotiation.

DOWNWARD NEGOTIATIONS

Mr. Early. Doctor, to what extent will there be downward negotiations in competing and non-competing grants, respectively, under the budget request?

Dr. Kirschstein. Overall, both competing and non-competing grants will be reduced 12.7 percent from Council-recommended levels under the FY 1991 budget request.

Mr. Early. What effect have these downward negotiations had on your grantees?

Dr. Kirschstein. Many of our grantees have reported that the reductions of 10 percent or greater in grant budgets, over the past two years, have slowed the pace of their research. This is primarily due to having to cut back on the time and effort of laboratory technicians as well as on some equipment and supplies.

RESEARCH CENTER GRANTS

Mr. Early. The budget justification indicates that you plan to fund one less research center in FY 90. What accounts for this reduction?

Dr. Kirschstein. The NIGMS funded 10 research center grant awards in FY 1989, but will only fund 9 such awards in FY 1990. The missing award was a research center grant in the field of molecular pathology provided to Yale University. The principal investigator on this award, Nobelist George Palade, recently moved to the University of California, San Diego, where he assumed new administrative duties.

Thus, he did not request the transfer of the center grant award to his new institution. Given the current budget situation, the NIGMS chose not to fund a replacement center grant, so that more support could be provided for research project grants.

Mr. Early. Will there be downward negotiations in your Institute's centers? If so, what is the level of downward negotiations for competing and non-competing centers?

Dr. Kirschstein. The Institute's budget request for FY 1991 assumes downward negotiations of 7 percent for both competing and non-competing research center grant awards.

Mr. Early. Doctor, over the past 10 years, the number of research centers supported by NIGMS has declined from 23 in 1982 to 9 in FY90 and FY91. To what is this decline attributable? Did these centers no longer make an important contribution to the NIGMS research program?

Dr. Kirschstein. The decline in NIGMS research center grant support is attributable to several factors: (1) the Institute's belief that its mission of supporting basic research is best accomplished through individual investigator-initiated research project grants; (2) the NIH policy of giving the highest priority for the allocation of available funds to research project grants--a policy with which the NIGMS agrees; and (3) a requirement of the Institute that the scientific quality of any center grant being supported be the equivalent of the research project grants being supported.

The research center grants funded by the NIGMS, over the years, have made, and continue to make, important contributions to the Institute's research mission--primarily by encouraging clinical researchers and laboratory scientists to work together on novel high quality research projects. For the reasons noted above, however, the Institute has chosen to give priority to research project grant awards over research center grants within the funds made available. The scientific quality of the research project grant applications being received by the NIGMS is truly superb, and the Institute wants to fund as many of these applications as it possibly can, in order to maximize scientific progress.

Mr. Early. Were fiscal constraints the reason for the decline?

Dr. Kirschstein. As noted above, fiscal constraints represent one of the factors in the Institute's decision to reduce support for research center grants.

RESEARCH TRAINING

Mr. Early. Doctor, your budget request projects a modest increase in the number of research trainees for both FY 90 and FY 91. In what program areas will research training be increased?

Dr. Kirschstein. In FY 1990, the increases in research trainees will be in the Minority Access to Research Careers Program and in the Biotechnology Research Training Program, which is administered in the Pharmacological Sciences Program. In FY 1991, the entire increase in research trainees is in the Minority Access to Research Careers Program.

Mr. Early. Last year, the National Science Foundation projected a shortage of 675,000 scientists and engineers in the U.S. by the year 2006. Despite this, NIH support for research training has increased little. Your Institute's 1991 training budget, for example, provides for only 136 more trainees than your 1990 budget. Shouldn't we be doing more in this area?

Dr. Kirschstein. The NSF report does convincingly point to the prospect of personnel shortages in biomedical research as we approach the 21st century. And, given this projection, it would make sense to support additional research trainees. However, some difficult choices had to be made in developing the FY 1991 budget. Given these choices, we elected not to use the funds made available to the Institute to direct substantial increases to research training.

Despite this, the Institute was pleased that it was able to significantly increase its support for the Minority Access to Research Careers Program in FY 1991. This was done with the understanding, based on a number of reports, including the NSF report, that minorities must be encouraged to play an increasingly vital role in the Nation's biomedical research enterprise in the coming years.

PHYSICIAN RESEARCHERS

Mr. Early. Last year, an article appeared in Medical World News, which stated that "The ranks of physician researchers are dwindling to a degree that is dangerous to clinical progress." This article spoke of the importance of the Medical Scientist Training Program, funded by your Institute, in addressing this problem. But, one physician was quoted as saying this effort was only "A drop in the bucket" compared to the need. Doctor, how many individuals will you be able to support under this program in 1991?

Dr. Kirschstein. In FY 1991, 735 trainees will receive support under the Institute's Medical Scientist Training Program.

Mr. Early. In your professional judgment, how many should we be supporting? And, how much extra would this cost?

Dr. Kirschstein. In my professional judgement, we should be supporting 800 trainees under this program, or 65 more than are presently proposed. This would require an additional $3.0 million above the amount presently budgeted to fully fund 735 MSTP trainees.

BIOTECHNOLOGY RESEARCH TRAINING PROGRAM

Mr. Early. Bring us up to date on the new research training program in biotechnology. I know the program is only a little more than a year old, but can you give us some idea of how successful it has been?

Dr. Kirschstein. The NIGMS biotechnology research training initiative has been very successful, both in terms of the large number of applications received and the quality of the trainees being supported. As noted in a recent report issued by the Institute of Medicine/National Academy of Sciences, the continuing rapid growth of the American biotechnology industry has already created shortages of scientific personnel in some areas; and, given this trend, I believe this program will acquire increasing importance over the coming years.

Mr. Early. How many trainees do you plan to support in FY91, and how does this compare with the recommended number?

Dr. Kirschstein. The President's budget request provides approximately $4.3 million for the support of 190 biotechnology trainees in FY 1991, the same number of trainees being supported in FY 1990. This is 560 fewer trainees than the 750 recommended for 1991 by a panel of experts, called together at NIH two years ago.

USE OF ADDITIONAL FUNDS

Mr. Early. If an increase over the FY 91 request is provided, how would you use these additional funds? What would your priorities be?

Dr. Kirschstein. The Institute would use additional funds in two priority areas. In the research project area, we would increase the number of competing research grants funded, so that our award rate would move toward historical levels of 35-40 percent, and we would reduce the negotiated reductions imposed on grants so that cuts would not exceed 10 percent. In addition, in the research training area, we would increase the number of individual and institutional research trainees we support in order to move toward the numbers recommended by the National Academy of Sciences in its recent report. The amount of any increase would dictate to which of these priority areas additional funds would be directed.

LOST RESEARCH OPPORTUNITIES

Mr. Early. Will any significant new research initiatives or opportunities be lost or delayed by lack of funds in the FY91 budget?

Dr. Kirschstein. The President's budget request for NIGMS provides support for 819 new and competing renewal research project grant awards in FY 1991. This will allow the Institute to support a significant amount of exciting new research initiatives next year. However, since only about 26 percent of the approved applications received can be funded within the budget request, many other research opportunities would clearly be lost, or have to be deferred.

Mr. Early. Please provide, for the record, a list of these along with a brief description and the funding requirements associated with each.

Dr. Kirschstein. The descriptions below highlight a number of areas where future research opportunities hold promise because of important discoveries or recent developments. A total of approximately

$50 million in additional funds would be required to support 50 percent of approved competing applications in these and other similarly important research areas:

1. PEG Coating of Therapeutic Drugs: The FDA recently approved a successful new drug treatment for a rare genetic disease formally called "severe combined immunodeficiency disorder", but often referred to simply as the "Bubble Boy Disease". The key to the new treatment involves a process, developed by an NIGMS grantee, of coating the drug to be administered with a substance called polyethylene glycol, or PEG. This process protects the drug from being broken down by the body's natural defense systems before it can do its job. Pharmacologists now believe that, with further research, this new technology could successfully be applied to a wide range of therapeutic agents, including anti-cancer drugs and antibiotics, that currently have a short life span in the bloodstream, and thus are not as effective as they might be. Experts believe that the potential applications of the PEG coating process are almost limitless.

2. Use of Antibodies as Metalloenzymes: A great many naturally occurring enzymes in the body contain metal ions as essential components for their proper functioning. However, only recently have efforts related to the development of antibody-based enzymes containing metal ions been initiated. This emerging research field is considered to hold great promise for the development of drugs, drug carriers, and detoxicants, as well as useful synthetic reagents for the pharmaceutical and biotechnology industries. Immediate research opportunities in this area relate to the development of an enzyme important in the production of neurotransmitters that play a critical role in the normal functioning of the central nervous system.

3. Studies of the Elastin Gene: Elastin is the resilient protein found in the extendable tissues of the body, such as the skin, lungs, and blood vessels. A number of rare human hereditary diseases appear to be caused by improper regulation of the activity of the gene, which codes for elastin, and several researchers are interested in analyzing the role played by growth hormone and growth factors in the process of regulating the activity of this critical gene.

4. Contractile Structures in Non-Muscle and Developing Muscle Cells: Actin is a protein whose role in force generation and the production of movement within living cells is well documented. Its malfunction has been correlated to the occurence of several disease states, including cancer. Developments in the field of actin research suggest the need for further information on the assembly of this protein within cells, the mechanisms involved in stress fiber elongation, and the regulation of actin polymerization.

5. Newly Discovered Class of G-Proteins: G-proteins are essential membrane bound proteins, recognized to play an important role in cell to cell communication, thereby mediating the production of a wide range of chemicals critical to life-sustaining biological processes. Recently, a new class of G-proteins was discovered in human neutrophils, the white blood cells that are active in both inflammation and in the body's defense against invading microorganisms. Gaining a knowledge of the precise structure and function of these newly dis-

covered proteins could yield important benefits for understanding and treating a number of human disorders, particularly serious infectious diseases.

6. Volatile Anesthetics and Cardiac Function: Gaining an in-depth knowledge of how anesthetics work at the molecular level is a major goal of the NIGMS Pharmacological Sciences Program, since such knowledge provides important insights needed to improving clinical care. The volatile anesthetics, halothane, enflurane, and isoflurane, are general anesthetics widely used during major surgery. But, despite their relative safety, their use must be monitored since life-threatening complications can occur in certain types of patients, including those with cardiac disease. For this reason, new research studies are needed to elucidate the subcellular mechanisms involved in anesthetic-induced myocardial depression.

SUPPORT FOR RESEARCH IN CHEMISTRY

Mr. Early. The NIGMS is one of the two major supporters of all research in chemistry in the U.S. Why is it important for NIGMS to maintain vigorous support for research in chemistry?

Dr. Kirschstein. Because all life processes are manifestations of chemical changes, understanding the myriad chemical reactions that take place in living organisms, including in man, is necessary in order to understand both health and disease. In 1985, the National Academy of Sciences recognized this and issued a report called Opportunities in Chemistry, which made the point that this is a particularly promising time to support research in chemistry. This is because recent advances in research instrumentation and techniques now allow scientists to probe and understand the elemental steps of chemical change, and, at the same time, to deal with extreme molecular complexity. This means that biology and chemistry are now intertwined disciplines. For example, scientists can synthesize tailored molecules to test hypotheses about the structure and function of hormones, enzymes, and receptor proteins; to rationally design new therapeutic agents; and to explore the function of selected areas of genetic material. In addition to expanding our knowledge of fundamental life processes by applying chemistry in modern molecular biological studies, the findings emerging from such research will undoubtedly strengthen the underpinnings of the chemical and biotechnology industries, both critical to the Nation's economic health.

IMMUNOGENETICS

Mr. Early. I understand that there has been an important breakthrough in the field of immunogenetics. Tell us a little about this. Why is this advance considered so important?

Dr. Kirschstein. Lymphocytes of the immune system produce antibodies which recognize millions of different foreign molecules. This diversity of the immune system is the key to man's defense against chemical and microbial invaders. Antibodies are protein molecules whose synthesis is directed by corresponding gene units. The order in which these gene segments combine and rearrange is what accounts for antibodies being able to attack diverse invaders. Recently, researchers at the Whitehead Institute for Biomedical Research discovered a gene, termed RAG-1, which controls the recombination of these gene segments by an enzyme called recombinase. This discovery will permit us to understand how lymphocyte genes rearrange in an orderly fashion as part of the normal development of the immune system. When this normal development fails to occur, severe combined immunodeficiency may result. Furthermore, when immunoglobulin genes recombine inappropriately, leukemia and lymphomas may result. Improper assembly of lymphocyte receptor genes could result in auto-immune disorders. Thus, discovery of RAG-1 will permit a better understanding of the normal immune system, which in turn provides the key to understanding what goes wrong in diseases of the immune system.

NATIONAL CENTER FOR HUMAN GENOME RESEARCH

Mr. Dwyer. This year, the National Center for Genome Research will begin its efforts in earnest.

To what extent will the Genetics Program supported by NIGMS be working with the new Human Genome Center?

Dr. Kirschstein. Although administration of the Genome Project has moved from NIGMS to the new National Center for Human Genome Research (NCHGR), these two components of NIH are continuing to work together in a number of ways. The major areas of interaction include administration of investigator-initiated research grants and research training activities, as well as joint consultation regarding the management of genetic resources.

The NIGMS supports untargeted, investigator-initiated research in the basic biomedical sciences, while the scope of NCHGR is more narrowly focused on the development and implementation of technologies for genome analysis, as well as the acquisition of chromosomal maps and genomic sequences of humans and certain model organisms. In spite of the fundamental differences between the missions of NIGMS and NCHGR, the programs are highly complementary. The Genetics Program of NIGMS will continue to support research on model systems that is designed to lead to a better understanding, and eventually prevention and treatment, of human genetic diseases. This research will include cytogenetic studies and structural studies on the human chromosomes, as well as research focused on understanding the biological significance of DNA sequences. There will undoubtedly continue to be areas of overlapping interest throughout the evolution of the Human Genome Project. Moreover, it is likely that one of the dividends of the Genome Project will be the discovery of novel sequence motifs that will open up new areas of basic genetic research that will fall within the purview of NIGMS.

The staffs of NIGMS and NCHGR are continuing to interact on a regular basis to coordinate research training activities. NIGMS has extensive experience in supporting interdisciplinary predoctoral and postdoctoral training in genetics. Although the NCHGR training programs will focus on specialized areas, such as acquisition and analysis of sequence data, it is likely that the established programs in NIGMS will serve as models for, and will complement, those being developed at NCHGR.

NIGMS supports two resources, GenBank, the nucleic acid sequence database, and the Human Genetic Mutant Cell Repository that will play essential roles in the Genome Project. The staffs of NIGMS, NCHGR, and the National Library of Medicine are working jointly to ensure that GenBank will be able to accommodate the ever-increasing volume of sequence data. Similarly, the Human Genetic Mutant Cell Repository is cooperating with NCHGR to ensure that cell lines needed by investigators working on the Genome Project will be available.

IMMUNOSUPPRESSANT DRUGS

Mr. Dwyer. Immunosuppressant drugs, such as cyclosporine, have played an important role in the success of organ transplantation; however, cyclosporine has a number of serious side effects.

What drugs are currently being investigated which would provide the benefits of cyclosporine, but not the side effects?

Dr. Kirschstein. Currently there are two drugs which are being used as immunosuppressants subsequent to transplantation--cyclosporine and a new drug, FK-506, developed by the Japanese. While FK-506 initially appeared to have far fewer toxicities than cyclosporine, with time and experience it has been shown to possess its own set of toxicities no less drastic than those seen with cyclosporine. This is not surprising when one realizes that the receptor molecules to which both drugs bind, while different, actually have the same enzymatic activity within the cell. Since there is a tremendous market for a non-toxic immunosuppressant drug, there are a number of investigators both in academia and in industry looking for alternative compounds.

Mr. Dwyer. Can cyclosporine be altered in any way to alleviate or minimize its toxic effects?

Dr. Kirschstein. Investigators are currently using a rational approach to drug design to define the structure of the cyclosporine receptor and then to design drugs which will fit a specific segment of the receptor precisely. They thereby hope to eliminate some of the side effects that may result from the action of other parts of the cyclosporine molecule, which are not necessary for the immunosuppressive effects or for the nonselective binding of cyclosporine to other molecules. A group of scientists at Yale University are currently using a combination of nuclear magnetic resonance spectroscopy, biochemistry, synthetic organic chemistry, and computer modelling to identify structural aspects of the cyclosporine receptor, use that information to build a molecule, test that molecule for immunosuppressant activity, and then use the information derived from this round of experiments to alter and improve the immunosuppressant activity of the molecule until the best drug can be developed.

NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION

Mr. Dwyer. Public Law 100-607 established a National Center for Biotechnology Information, NCBI, at the National Institutes of Health (NIH), within the National Library of Medicine. NCBI's responsibilities include integrating existing data bases, developing new computer analysis programs, and improving data access.

To what extent has the NIGMS been involved in the establishment of the NCBI?

Dr. Kirschstein. Beginning with the discussions that eventually led to the formation of the NCBI, NIGMS has been most supportive. Because many NIGMS grantees are heavily dependent on databases, such as GenBank, the Protein Identification Resource, and the Brookhaven Crystallographic database, and because NIGMS has been a lead agency in supporting the research that has led to the formation of the biotechnology industry, NIGMS has supported the creation of the NCBI as a means of ensuring that information relevant to the field of biotechnology is made available and that appropriate links are established among biotechnology related databases. To this end, in 1986, Dr. James Cassatt, a member of the NIGMS staff and the project officer for the GenBank contract, served on a National Academy of Sciences committee that evaluated the need for the dissemination of biotechnology information. Many of the recommendations from that committee were followed in establishing the NCBI. In general, NIGMS has welcomed the establishment of the NCBI to provide a focus for the information resources needed by the field of biotechnology.

In addition, it is anticipated that the responsibility for the administration of GenBank will be transferred to the NCBI at the expiration of the current contract in September 1992. NIGMS staff are working in close collaboration with the NCBI and the National Center for Human Genome Research to ensure continuity of service and that the needs of the scientific community will continue to be served.

JUSTIFICATION OF THE BUDGET ESTIMATES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

FY 1991 Budget — Page No.

Appropriation language and explanation of language change... 202
Amounts available for obligation........................... 203
Budget mechanism table..................................... 204
Crosswalk tables... 206
Summary of changes... 209
Budget authority by activity............................... 211
Budget authority by object................................. 212
Significant items in House and Senate Appropriations Committee report...................................... 214
Authorizing legislation.................................... 216
Appropriations history..................................... 217

Justification:

A. General statement..................................... 219
B. Program accomplishments................................ 222
C. AIDS research and training program..................... 226
D. Cellular and molecular basis of disease................ 228
E. Genetics... 232
F. Pharmacological sciences............................... 237
G. Biophysics and physiological sciences.................. 242
H. Minority biomedical research support................... 246
I. Minority access to research careers.................... 249
J. Intramural research.................................... 254
K. Research management and support........................ 256
L. Detail of permanent positions.......................... 257
O. Advisory and assistance services....................... 259

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

For carrying out section 301 and title IV of the Public Health Service Act with respect to general medical sciences ($691,866,000) *$745,494,000*.

(Departments of Labor, Health and Human Services, and Education and Related Agencies Appropriations Act, 1990.)

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Amounts Available for Obligation 1/

	1989 Actual	1990 Appropriation	1991 Estimate
Appropriation	$690,653,000	$691,866,000	$745,494,000
Enacted administrative reduction	-8,304,000	-588,000	---
Sequester order	---	-9,496,000	---
Subtotal, adjusted appropriation	682,349,000	681,782,000	745,494,000
Real transfer to the Health Resources and Services Administration for AZT grants	-136,000	---	---
Comparative transfer from:			
Division of Research Resources for MBRS program	29,199,000	30,254,000	---
Office of the Director, NIH for FTE increase	106,000	---	---
Comparative transfer to:			
National Center for Human Genome Research for the Genome program	-27,569,000	---	---
Division of Research Resources for administrative costs of RCMI grants	-23,000	---	---
Fogarty International Center for passport activity	-6,000	-6,000	---
Subtotal, adjusted budget authority	683,920,000	712,030,000	745,494,000
Unobligated balance lapsing	-79,000	---	---
Total, Obligations	683,841,000	712,030,000	745,494,000

1/ Excludes the following amounts for reimbursable activities carried out under this account: 1989 - $3,874,000; 1990 - $5,256,000; 1991- $5,150,000.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Budget Mechanism

(Dollars in thousands)

	1989 Actual		1990 Appropriation 1/		1991 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research grants:						
Research projects						
Noncompeting	2,473	$413,516	2,559	$442,597	2,381	$432,323
Admin. supplemental	(35)	1,451	(17)	642	(17)	642
Competing						
Renewal	355	72,002	289	63,693	404	92,399
New	425	53,713	341	47,419	407	57,108
Supplemental	8	1,250	7	1,624	8	1,872
Subtotal, competing	788	126,965	637	112,736	819	151,379
Subtotal, research projects	3,261	541,932	3,196	555,975	3,200	584,344
Research Centers						
Pharmacological sciences	3	1,984	2	1,762	2	1,742
Anesthesiology	1	795	1	949	1	969
Trauma and burn	5	3,009	6	4,239	6	4,239
Molecular pathology	1	731				
Subtotal research centers	10	6,519	9	6,950	9	6,950
Other research						
Research career program	17	736	19	868	19	868
MBRS	98	28,147	98	29,794	98	32,326
Other	122	4,107	84	4,452	84	4,452
Subtotal, other research	237	32,990	201	35,114	201	37,646
Total, research grants	3,508	581,441	3,406	598,039	3,410	628,940

Training:						
Individual awards						
Noncompeting	299	7,228	226	6,049	356	9,820
Competing						
Renewal						
New	181	4,059	266	7,580	155	4,200
Subtotal, individual	480	11,287	492	13,629	511	14,020
Institutional awards						
Noncompeting	2,721	53,463	2,232	48,005	2,983	61,529
Competing						
Renewal	348	7,125	881	17,040	483	9,504
New	153	3,406	265	4,117	29	597
Supplementals						
Subtotal, institutional	3,222	63,994	3,378	69,162	3,495	71,630
Total, training	3,702	75,281	3,870	82,791	4,006	85,650
Research and development contracts	5 FTEs	5,670	7 FTEs	5,826	7 FTEs	5,835
Intramural research	18	957	22	1,052	22	1,099
Research management and support	145	20,571	151	22,855	154	23,970
Extramural Construction				1,467		
TOTAL	163	683,920	173	712,030	176	745,494
HIV/AIDS	[2]	[10,901]	[2]	[14,614]	[2]	[15,487]

1/ Includes approximately $1,467,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

CROSSWALK - 1989 ACTUAL

(Dollars in thousands)

	Research Grants			Training Programs					
	Research Projects	Research Centers	Other Research	Individual	Institutional	Research and Development Contracts	Intramural Research	Research Management & Support	Total
Cellular and molecular basis of disease	$167,814	$731	$2,572	$2,315	$16,285	$35			$189,752
Genetics	189,073		484	5,074	9,482	5,431			209,544
Pharmacological sciences	83,049	2,779	97	1,025	5,559	10			92,519
Biophysics and physiological sciences	101,996	3,009	1,690	1,566	24,922	194			133,377
Minority biomedical research support			28,147						28,147
Minority access to research careers				1,307	7,746				9,053
Intramural research							$957		957
Research management and support								$20,571	20,571
Total	541,932	6,519	32,990	11,287	63,994	5,670	957	20,571	683,920

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

CROSSWALK - 1990 APPROPRIATION 1/

(Dollars in thousands)

	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management & Support	Extramural Construction	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional					
Cellular and molecular basis of disease...........	$173,747		$2,431	$2,228	$15,463	$35				$193,904
Genetics......................	188,601		557	4,417	9,515	5,510				208,600
Pharmacological sciences.....	84,697	$2,711	132	2,857	8,746	12				99,155
Biophysics and physiological sciences..................	108,930	4,239	2,200	2,714	26,181	269				144,533
Minority biomedical research support......................			29,794							29,794
Minority access to research careers.....................				1,413	9,257					10,670
Intramural research...........							$1,052			1,052
Research management and support.....................								$22,855		22,855
Extramural Construction......									$1,467	1,467
Total........................	555,975	6,950	35,114	13,629	69,162	5,826	1,052	22,855	1,467	712,030

1/ Includes approximately $1,467,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

CROSSWALK - 1991 ESTIMATE

(Dollars in thousands)

	Research Grants			Training Programs		Research and Development Contracts	Intramural Research	Research Management & Support	Total
	Research Projects	Research Centers	Other Research	Individual	Institutional				
Cellular and molecular basis of disease	$184,340		$2,495	$2,228	$15,463	$35			$204,561
Genetics	194,862		576	3,599	10,333	5,510			214,880
Pharmacological sciences	89,048	$2,711	104	2,857	8,746	12			103,478
Biophysics and physiological sciences	116,094	4,239	2,145	2,749	26,316	278			151,821
Minority biomedical research support			32,326						32,326
Minority access to research careers				2,587	10,772				13,359
Intramural research							$1,099		1,099
Research management and support								$23,970	23,970
Total	584,344	6,950	37,646	14,020	71,630	5,835	1,099	23,970	745,494

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Summary of Changes

1990 Estimated Budget Authority	712,030,000
1991 Estimated Budget Authority	745,494,000
Net change	+33,464,000

	1990 Current Estimate Base		Change from Base	
	Pos. (FTEs)	Budget Authority	Pos. (FTEs)	Budget Authority
Changes:				
A. Built-in:				
1. Within-grade pay increase		$8,172,000		+$54,000
2. Annualization of pay raise		8,172,000		+69,000
3. Federal Employee Compensation Fund increase		33,000		+1,000
4. Cost of one extra day of pay		8,172,000		+29,000
5. FTS rate increase		92,000		+4,000
6. Cost of 1991 pay raise		8,172,000		+281,000
7. Increased cost of centrally furnished services		6,157,000		+374,000
8. Service and Supply Fund increase		4,306,000		+10,000
9. Increased costs of supplies materials & other expenses		9,578,000		+320,000
10. DHHS Working Capital Fund		671,000		-33,000
Subtotal				+1,109,000
	No.	Amount	No.	Amount
B. Program:				
1. Research projects:				
a. Noncompeting	2,559	443,239,000	-178	-10,274,000
b. Competing	637	112,736,000	+182	+38,643,000
Total	3,196	555,975,000	+4	+28,369,000

Summary of Changes--continued

	1990 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
Changes:				
3. Other research.................	201	35,114,000	---	+2,532,000
4. Training........................	3,870	82,791,000	+136	+2,859,000
5. Research and dev. contracts....	7	5,826,000	---	+9,000
6. Extramural construction........	---	1,467,000	---	-1,467,000
	Pos. (FTEs)	Budget Authority	Pos. (FTEs)	Budget Authority
7. FTE increase in research management and support.........	(173)	8,172,000	(+3)	+53,000
Subtotal.......................				+32,355,000
Total change..................				+33,464,000

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Budget Authority by Activity

(Dollars in thousands)

	1989 Actual		1990 Appropriation 1/		1991 Estimate	
	FTEs	Amount	FTEs	Amount	FTEs	Amount
Cellular and molecular basis of disease....	---	$189,752	---	$193,904	---	$204,561
Genetics..............	---	209,544	---	208,600	---	214,880
Pharmacological sciences............	---	92,519	---	99,155	---	103,478
Biophysics and physiological sciences....	---	133,376	---	144,533	---	151,821
Minority biomedical research support	---	28,147	---	29,794	---	32,326
Minority access to research careers....	---	9,053	---	10,670	---	13,359
Intramural research...	18	952	22	1,052	22	1,099
Research management and support.........	145	20,498	151	22,855	154	23,970
Extramural construction.	---	---	---	1,467	---	---
Total Obligations	163	683,841	173	712,030	176	745,494
Unobligated balance lapsing.............		79		---		---
Total, Budget Authority.........	163	683,920	173	712,030	176	745,494
HIV/AIDS..............	[2]	[10,901]	[2]	[14,614]	[2]	[15,487]

1/ Includes approximately $1,467,000 to be transferred to other accounts for extramural construction in accordance with Public Law 101-166.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Budget Authority by Object

	1990 Appropriation	1991 Estimate	Increase or Decrease
Total number of full-time permanent positions	150	153	+3
Total compensable work years: Full-time equivalent employment	173	176	+3
Average ES salary	$76,241	$86,534	+10,293
Average GS grade	9.4	9.4	---
Average GS salary	$36,470	$37,418	+948
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	$74,813	$76,578	+1,945
Personnel compensation:			
Full-time permanent	$5,935,000	$6,252,000	+$317,000
Other than full-time permanent	879,000	925,000	+46,000
Other personnel compensation	160,000	168,000	+8,000
Subtotal, personnel compensation	6,974,000	7,345,000	+371,000
Personnel benefits	1,198,000	1,261,000	+63,000
Benefits for former personnel	6,000	6,000	---
Travel and transportation of persons	287,000	287,000	---
Transportation of things	24,000	24,000	---
Rent, communications, and utilities	234,000	238,000	+4,000
Printing and reproduction	400,000	400,000	---
Other services:			
Project contracts	5,826,000	5,835,000	+9,000
Centrally furnished services	5,296,000	5,901,000	+605,000

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Budget Authority by Object--continued

	1990 Appropriation	1991 Estimate	Increase or Decrease
Standard level user charge.........	861,000	630,000	-231,000
Other..............................	6,884,000	7,234,000	+350,000
Supplies and materials...............	113,000	113,000	---
Equipment............................	1,630,000	1,630,000	---
Grants, subsidies, and contributions.	682,297,000	714,590,000	+32,293,000
Total....................	712,030,000	745,494,000	+33,464,000

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Significant Items in House and Senate Appropriations Committee Report

Item

1990 House Report	Action taken or to be taken
1. The Committee would like to receive, prior to next year's hearings, a report from the NIH which outlines the long term plans for training needs and addresses where the specific gaps exist in current training efforts to meet these needs (page 70).	1. The requested report has been prepared and forwarded to the Committee.
2. The Committee is pleased with the success of the MARC Program in attracting minority students into biomedical research (page 70).	2. The NIGMS is likewise pleased with the continued success of the MARC Program. It is noted that the President's FY 1991 budget request provides approximately $13.4 million for this Program, a 25 percent increase over the FY 1990 estimate.
3. The Committee requests NIGMS to explore the feasibility of extending the MARC Honors Undergraduate Program into the freshman year of college and report to the Committee prior to the FY 1991 hearings (page 70).	3. The requested report has been prepared and forwarded to the Committee.
4. The Committee is fully supportive of this Institute's (NIGMS) other large minority research initiative, the Minority Biomedical Research Support (MBRS) Program, and has added $1.4 million to expand this program. This is in addition to amounts for the MBRS program expected to be transferred from the Division of Research Resources. The Committee is also pleased that NIH is expanding its minority programs and the addition provided in the bill should help finance these initiatives (page 70).	4. The additional funds provided for the MBRS Program in FY 1990 will be used to fund needed increases in the salaries of students working on research activities at MBRS-supported institutions.

Item

1990 Senate Report	Action taken or to be taken
1. The committee understands that NIH has proposed to transfer responsibility for directing this rapidly growing project (the Human Genome Project) to a new National Center for Human Genome Research, the creation of which is currently awaiting departmental approval. The Committee intends to await a request and recommendation on this matter before taking action to transfer this program out of the NIGMS (page 134).	1. The National Center for Human Genome Research was formally established by the Secretary on October 1, 1989. The Committee has been notified of the Department's desire to transfer all funds and responsibilities associated with the Human Genome Project from the NIGMS to the new Center.
2. Research training - In 1989, the NIGMS established a new research training program in biotechnology...The Committee strongly urges NIGMS to utilize nursing knowledge and expertise by systematically ensuring that professional nurses are involved in its activities and programs (page 136).	2. The NIGMS has been in contact with the American Nursing Association regarding the possible appointment of professional nurses to the NAGMS Council, as well as to other Institute committees and advisory groups.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	1990 Amt. Authorized	1990 Appropriation	1991 Amt. Authorized	1991 Budget Request
Research and Investigation	Section 301	42 241	Indefinite	$629,239,000	Indefinite	$659,844,000
National Institute of General Medical Sciences	Section 461	42 285k 289h	Indefinite		Indefinite	
National Research Service Awards	Section 487	42 288	Such Sums as Necessary 1/	82,791,000	Authorizing Legislation to be Requested 1/	85,650,000
Total Budget Authority.				712,030,000		745,494,000

1/ This training authority is shared with the research training programs of the Alcohol, Drug Abuse and Mental Health Administration.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Appropriations History

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1982	300,257,000 2/	360,561,000	354,138,000	339,862,000
1983	345,621,000	367,009,000	372,114,000	369,803,000
1984	383,139,000	363,444,000 3/	370,245,000 3/	415,937,000
1985	423,853,000	412,987,000 4/	495,150,000	482,909,000
1986	458,484,000	455,593,000 5/	510,872,000	514,765,000
1986 Sequester	---	---	---	-22,135,000
1987	471,533,000	576,562,000	565,271,000	570,916,000
1988	482,004,000	666,037,000 6/	650,617,000	632,676,000
1989	676,728,000 7/	623,087,000 8/9/	690,653,000 8/	690,653,000
1990	766,421,000 10/	692,639,000 11/	752,939,000 12/	691,278,000 13/
1990 Sequester	---	---	---	-9,496,000
1991	745,494,000 11/			

1/ Reflects enacted supplementals, rescissions and reappropriations.

2/ Reflects the September Amendment; the original request was $341,201,000.

3/ Excludes $48,000,000 in NRSA training programs not considered.

4/ Excludes $48,446,000 in NRSA training programs not considered.

5/ Excludes $57,721,000 in NRSA training programs not considered.

6/ Does not include funding for AIDS research. Consolidated at the Secretary's level.

7/ Does not include funding for AIDS research ($11,100,000). Proposed for consolidation at the Office of the Assistant Secretary for Health.

8/ Includes $11,100,000 for AIDS research.

9/ Excludes $69,841,000 in NRSA training programs not considered.

10/ Excludes funds for AIDS research proposed for consolidation in the Office of the Assistant Secretary for Health. Includes funds for the Human Genome Research Initiative.

11/ Includes funds for AIDS research and the Minority Biomedical Research Support Program which was transferred from the Division of Research Resources. Excludes funds for the Human Genome Research Initiative to be considered under a separate new appropriation account.

12/ Includes funds for AIDS research and funds for the Human Genome Research Initiative.

13/ Includes funds for AIDS research and the Minority Biomedical Research Support Program which was transferred from the Division of Research Resources. Excludes funds for the Human Genome Research Initiative and an enacted administrative reduction of $588,000.

Justification

National Institute of General Medical Sciences

	1990 Appropriation		1991 Estimate		Increase or Decrease	
	FTEs	BA	FTEs	BA	FTEs	BA
Total...	173	$712,030,000	176	$745,494,000	+3	$33,464,000
AIDS....	(2)	(14,614,000)	(2)	(15,487,000)	(-)	(+873,000)

General Statement

The National Institute of General Medical Sciences (NIGMS) supports research basic to the understanding of life processes. Such understanding is essential to the eventual solution of specific disease-related problems. A case in point is the recent finding of the gene for cystic fibrosis, which, as noted in the journal, Science, started with basic research--much of it supported by NIGMS--"that made it possible to search for a genetic needle in a haystack of DNA bases."

Another indication of the high quality and broad applicability of research supported by NIGMS is found in the numerous honors and awards given to Institute grantees each year. In 1989, the Nobel Prize in chemistry was shared by two long-time grantees, Dr. Thomas R. Cech of the University of Colorado at Boulder and Dr. Sidney Altman of Yale University. The 1989 Lasker Award for basic medical research was won by Dr. Alfred G. Gilman of the University of Texas Southwestern Medical Center, a long-time grantee who is also a graduate of the NIGMS Pharmacology Research Associate Program. President Bush recently awarded National Medals of Science to two NIGMS grantees and National Medals of Technology to two other grantees. In addition, 14 current and 8 former NIGMS grantees were among the 60 prominent scientists elected in 1989 to the prestigious National Academy of Sciences.

Both the Nobel Prize and the Lasker Award recognized major advances made by NIGMS grantees in the broad area of biorelated chemistry. NIGMS funds the bulk of the NIH-supported research in basic chemistry, and is one of the two major supporters of all research in chemistry in the United States.

Working independently, the Nobel winners, Drs. Cech and Altman each showed that the genetic material, RNA, which had previously been thought to have a somewhat passive role in the transmission of hereditary information, has the ability to act as an enzyme. Before their discovery, one of the central assumptions of biology had been that all enzymes, which catalyze or speed up various chemical reactions, are proteins. This startling discovery has led to a totally new and unexpected concept of the role of RNA in both genetic processes and in the chemistry of bodily processes.

The Lasker awardee, Dr. Gilman has made a number of significant findings in his quest to understand how a cell perceives and reacts, in a coordinated way, to the thousands of messages that bombard it. Most importantly he has been the primary contributor to our understanding of "G-proteins," which serve as intermediaries between incoming signals, such as hormones, and the cellular proteins that eventually respond to them.

Another NIGMS-supported scientist working in the area of basic chemistry is Dr. Elias J. Corey of Harvard University. He has developed a family of more than 20 totally synthetic enzymes that he calls "chemzymes." According to an article in the journal, Science, chemzymes are "among the most intriguing innovations of the decade." These man-made chemzymes are small molecules that catalyze certain reactions quickly and in such a way that only a biologically effective product is made. Moreover, they are produced by "rational" molecular design--that is, Dr. Corey and his coworkers start out with studies that lead to an understanding of the chemical mechanisms involved in a particular reaction. Then they synthesize molecules with exactly the properties needed to cause the desired effect. This system provides much greater control over the chemical reactions, avoids the synthesis of unwanted byproducts, and should help develop many therapeutic compounds more quickly and less expensively than is now possible.

To stimulate studies in basic chemistry that have the potential to contribute to AIDS-targeted drug development, NIGMS announced, in 1989, that new funds were available to expand and extend existing programs in this area. The aim is to advance state-of-the-art chemical design and methodology and to develop approaches to targeted drug design, which can then be applied to produce specific therapeutic agents which might be available for use in clinical studies.

Also, in 1989, NIGMS significantly enlarged the scope of its minority research and research training support efforts, when it took over administration of the Minority Biomedical Research Support (MBRS) Program from the NIH Division of Research Resources. The MBRS Program provides research grant support to colleges, universities, and health professional schools with substantial minority enrollments. These grants support research by faculty members, strengthen the institutions' biomedical research capabilities, and provide opportunities for students to work as part of a research team.

In addition, NIGMS continues to support the highly successful Minority Access to Research Careers (MARC) Program, which helps minority institutions improve their science curricula and funds research training for outstanding students at these institutions. MARC trainees also spend time doing research at leading academic and industrial settings throughout the country.

Beyond this, NIGMS is actively supporting the recently established NIH-wide initiative aimed at increasing the number of minority individuals who participate in ongoing NIH-funded research projects. In the first few months of this program, NIGMS received 39 applications from current grantees, requesting supplementary funds to support minority graduate students, undergraduate students, postdoctoral fellows, and junior faculty members on their projects. Thus far, 22 awards have been made, primarily to graduate students.

The NIGMS research training programs serve the biomedical community by providing critically needed new researchers who have received broad, multidisciplinary training. NIGMS trainees, such as those whose research is described in the program accomplishments section below, often make significant contributions to the work in their laboratories and to the overall advancement of scientific knowledge. Many of the scientists who are now at the forefront of their fields--scientists such as Drs. Cech and Gilman--received their training through NIGMS-supported training programs.

In addition to its minority-focused and traditional multidisciplinary programs, the Institute has several other special training programs--the Medical Scientist Training Program (MSTP), the biotechnology training program, and the Pharmacology Research Associate Training (PRAT) Program.

Overall Budget Policy

The NIGMS budget request for 1991 continues to emphasize the support of investigator-initiated research project grants. The budget request is $745,494,000, which represents an increase of $33,464,000 over the FY 1990 estimate. Included are funds related to AIDS. The FY 1991 estimate for AIDS is $15,487,000.

The request, excluding AIDS, will support 815 competing research project grants at an average cost of $184,752. This represents a 6.2 percent increase in funds over FY 1990 and a 12.7 percent downward negotiation from council-recommended levels. The request will support 2,365 noncompeting research project grants at an average cost of $179,112. This represents a 4.5 percent increase in funds over FY 1990 and a 12.7 percent downward negotiation from council-recommended levels.

With the high priority being placed on minority programs in FY 1991, the Minority Biomedical Research Support Program will total $32,326,000, an increase of 8.5 percent over FY 1990. Similarly, the only training program to receive an increase will be the Minority Access to Research Careers Program. For FY 1991, the request for MARC is $13,359,000 an increase of 25 percent over FY 1990.

Included in this request are built-in administrative cost increases for both Intramural Research and Research Management and Support. In addition, the request will provide support for three additional full-time equivalents (FTEs).

The request will fund all other extramural mechanisms at the FY 1990 level. This represents 9 research centers, 19 research career awards, 84 other research projects, 3,295 research trainees (excluding MARC) and 7 research and development contracts.

Program Accomplishments

Genetics and Cancer Connection Clarified

The genetic events that precede the onset of some kinds of cancer have been the subject of intense scrutiny for years. To date, researchers have identified about 50 genes that, if altered or mutated, permit a cell to divide continuously--a hallmark of cancer. Like most other genetic material, these "oncogenes" code for the production of proteins, substances that perform most of the work in a cell and that make up its bulk. Just how the proteins made by oncogenes countermand the cell's normal control of growth is not completely understood.

Recently, however, a group of researchers led by NIGMS grantee Dr. Jasper Rine of the University of California, Berkeley, discovered an unexpected connection between cholesterol synthesis and the ability of an oncogenic protein found in colorectal and pancreatic cancers to trigger cell division. This finding is the first to link cholesterol synthesis and the initiation of cancer. It not only helps scientists understand the processes that lead to cancer, but it also has prompted the idea that cholesterol-lowering drugs might find a place in the arsenal of therapeutic approaches for treating cancer.

Another group of scientists has found that the genetic analysis of cells from cancers of the colorectal areas of the intestinal tract can provide clues to the probable course of this common and frequently fatal cancer. This research was led by Dr. Bert Vogelstein at The Johns Hopkins University School of Medicine, whose team included two postdoctoral fellows supported by NIGMS training grants. The scientists examined samples of both cancerous and normal colon cells and found that portions of two chromosomes were missing in over 75 percent of the cancerous cells, but not in the normal cells. Moreover, patients with significant chromosomal deletions were more likely to have a poorer prognosis than those whose chromosome complement was complete. Thus, this work might eventually provide a molecular tool for improving predictions regarding the prognosis of patients with colorectal cancer.

Our understanding of how oncogenes work was advanced this year by an NIGMS grantee who is studying the structure and function of a protein that acts as a receptor for the thyroid hormone. Dr. Ronald Evans at the Salk Institute for Biological Studies showed that the oncogenic version of the gene that codes for the thyroid receptor appears to block the body's normal response to thyroid hormone. Such blockage could mark the beginning of a process that could lead to cancer. This is the first report of an oncogene that works by inactivating, rather than activating, processes that normally control cell growth. Although it is too early to tell just what implications the discovery of this new type of oncogene may have for the understanding and eventual prevention and treatment of cancer, it is possible that this work may aid in the diagnosis of malignancies.

Basic Cell Research Helps Quest for AIDS Therapies

In the hope of ameliorating the AIDS epidemic, scientists from diverse medical disciplines are seeking treatments for this dread disease. But basic research on the fundamentals of cellular function can also contribute to an understanding of AIDS and point the way toward new therapies.

A case in point is the work of Dr. Melvin Simpson, an NIGMS grantee at the State University of New York at Stony Brook. His long-time study of normal cell functions is now advancing the fight against AIDS. Dr. Simpson's research on the drug azidodeoxy-thymidine (AZT) has revealed some of the reasons why this compound, the major chemotherapy for AIDS, is toxic to normal cells. AZT's toxicity appears to be due to its effect on cell organelles called mitochondria, which make the energy-containing compounds that cells must have to function. Dr. Simpson has used this knowledge to identify substances that act like AZT but that may be less toxic to normal cells. These agents are currently being tested and may lead to better therapies for AIDS.

Protein's Role in Alzheimer's Disease Postulated

Scientists supported by NIGMS have discovered a possible link between a protein called alpha-1 antichymotrypsin (ACT) and Alzheimer's disease. NIGMS grantee, Dr. Huntington Potter at Harvard University has found that ACT is not only an integral part of the beta amyloid plaques present in the brains of people with Alzheimer's disease, but also that it is present in these plaques at high levels. Since ACT works elsewhere in the body to inhibit the activity of enzymes that break down other proteins, Dr. Potter and his colleagues speculate that an excess of ACT might prevent enzymes in the brain from breaking down the plaque-forming beta amyloid protein. In this way, ACT--which normally should protect the brain from uncontrolled protein breakdown--may upset the delicate balance between enzymes and inhibitors and contribute to the development of Alzheimer's disease.

New Type of Microscope Used to "See" Minute DNA Details

The scanning tunnelling microscope (STM) is a valuable tool that is able to produce direct images, at the atomic level, of a wide range of complex surfaces. Until very recently, however, attempts to use STM to study biological specimens, such as segments of the genetic material, DNA, were unsuccessful. Now, NIGMS grantees Drs. Victor Bloomfield and D. Fennell Evans of the University of Minnesota have succeeded in using the STM to obtain very good atomic-level images of DNA. These researchers think that the special method they developed of preparing the DNA specimens helped to make these images possible. In addition, the scientists sharpened their pictures by lining up several DNA molecules in a manner that gives more stability to the structure being studied.

Scanning tunnelling microscopy has several advantages over electron microscopy and X-ray diffraction analysis, the two methods most commonly used to study molecular structure. Specimen preparation for electron microscopy destroys much of the detail of the biological material. X-ray diffraction provides information that, while derived from a large volume of data, basically is an average of the measurements performed. In contrast, the STM can provide details about specific areas by permitting direct imaging of individual atomic sites.

In their recent studies, Drs. Bloomfield and Evans were able to actually visualize the two separate strands of the DNA double helix wrapping around each other. The images they obtained appear to show specific DNA structural features called the major and minor grooves. The researchers also have made images of a rare, but scientifically very interesting form of DNA known as Z-DNA.

The ability to visualize DNA at high resolution with scanning tunnelling microscopy is of importance because a number of aspects of gene regulation, including the binding of protein to DNA, depend on minute variations in the molecular structure of the DNA. Understanding DNA structure in relation to its activity may, in turn, improve knowledge regarding the mechanisms by which DNA interacts with such substances as carcinogenic chemicals or drugs, and could thus have important implications for human health.

Clues Found to Genetic Differences in Drug Response

Pharmacologists studying the appropriate dosage levels of propranolol, a drug widely used to treat high blood pressure, know that the response to this drug varies among racial groups. For instance, blood pressure can be controlled in Chinese patients with much lower propranolol doses than those required for individuals of European descent. Other studies indicate that many Blacks may need even higher doses of propranolol than other racial groups. Since scientists believe these differences in drug sensitivity may be hereditary, NIGMS grantee Dr. Grant R. Wilkinson at Vanderbilt University has been studying the metabolism of the drug in various populations. These researchers have found that propranolol is metabolized by two separate, genetically determined pathways, making it the only drug so far identified that is metabolized by more than one system. This discovery is of clinical significance because of the implications for adverse interactions between propranolol and other drugs. In addition, further study may yield some very valuable information about the chemistry of the enzyme systems that are involved in these different metabolic pathways.

New Skin Cultivation Technique Improves Closure of Burn Wounds

The past decade has been marked by a number of major advances in the treatment of severe burn wounds. Scientists working with NIGMS support developed an artificial skin that can be used to close wounds until enough skin from non-burned sites can be harvested for grafting. Other researchers created a cell culture technique for growing a small sample of a patient's own skin cells into large sheets that can be grafted onto wounds. The major drawback of the latter technique is that the sheets of skin cells are extremely fragile, making them difficult to work with in the laboratory and operating room. Futhermore, they remain somewhat fragile and easily detach even after grafting.

Now, a team of NIGMS-supported scientists at the University of California, San Diego, led by Dr. John F. Hansbrough and including an NIGMS postdoctoral fellow, Dr. Matthew L. Cooper, has succeeded in developing an improved method for closure of burn wounds. In a clinical trial on four patients, the new substance yielded very promising results.

The researchers used collagen, a connective tissue protein, as the base layer of their wound covering. They "seeded" the collagen with connective tissue cells from patients with extensive burn injuries. On top of this they placed a layer of skin cells grown from a small sample of the patient's unburned skin. The resulting "sandwich" resembles the two major layers of the normal skin, with the lower layer giving the upper one added strength and stability and also promoting the growth of blood vessels and structural proteins into the wound covering. The researchers noted the formation of characteristic anatomical structures between the two layers of skin within 9 days after grafting. In contrast, the formation of such structures can take from a month to a year following the use of other skin substitutes. While the new technique is several years away from general use, it could represent a major advance in burn treatment by significantly reducing the time between injury and satisfactory, permanent wound closure. Shortening this time period decreases the chance of infection and promotes healing, largely by curtailing fluid loss.

AIDS Research Program

NIGMS AIDS Program

The NIGMS program of AIDS-related research is focused on efforts to develop new information regarding the three- dimensional structures of various proteins (macromolecules) involved in the pathology of AIDS, including, for example the protein that covers and protects the AIDS virus as it travels through the bloodstream in search of a host cell, as well as the proteins on the host cell to which the AIDS virus docks. Investigators believe that once the structures of such proteins are delineated, it will be possible to design antiviral compounds configured in such a way as to block the normal avenues of viral action. If, for example, a non-toxic chemical substance were to be developed with the proper shape, it could attach itself to the viral receptor proteins on the host cell, thereby making these receptors unvailable to the AIDS virus. The theory is that this process would end the replicative cycle of the AIDS virus before the disease stage begins.

The immediate objectives of the AIDS-related research by NIGMS supported investigators are to obtain sufficient quantities of AIDS-related proteins for study, to purify and develop crystals of the proteins, and to examine the crystals via the process of X-ray crystallography together with other techniques.

In the research training area, primary emphasis also has been given to structural biology, particularly to training related to the determination and analysis of the macromolecular structures. The Institute's FY 1989 support level for research training related to AIDS was $3.9 million, which funded 27 institutional predoctoral training grants and a total of 192 trainees. Individual postdoctoral fellowships in FY 1989 totalled 50, at a cost of approximately $1.2 million.

Recent Research Accomplishments

Research advances reported by NIGMS grantees over the past year include the following:

- Dr. Stephen Harrison of Harvard University reported success in developing the first crystals of CD4, the protein recognized to serve as the receptor for the AIDS virus on host cells. According to the investigators, this was a relatively low resolution structure, but prospects for improvement seem positive.

- Two groups, one from Agouron Pharmaceuticals and the other from the laboratory of Dr. Harold Varmus of the University of California at San Francisco, have reported progress on the expression and purification of the integration protein of HIV.

- In a related accomplishment, progress in obtaining small crystals of HIV reverse transcriptase--the protein that helps the AIDS virus change into its final, disease-producing form--was reported by Drs. Edward Arnold of Rutgers University, Stephen Hughes of the Frederick Cancer Research Facility, and Richard Dickerson of UCLA, working collaboratively.

- Chemical probes for examining proteins within the cellular membrane lipid bilayer have been identified by Dr. Fred Richards and his colleagues at Yale University as a possible means to identify the region of the fusion protein required for virus-host membrane fusion.

Research Plans

The FY 1991 request provides $15.5 million for research and research training related to AIDS. This estimate includes support for 20 research project grants, 242 trainees, and 2 research and development contracts.

The Institute's goals for 1991 are to: (1) continue support for a series of six ongoing structural biology studies begun in 1987; (2) provide support for additional studies in this area, based on the fact that the availability of the materials needed (scarce proteins) has expanded to the point that new research teams and new opportunities may be identifiable; and (3) support studies in basic chemistry related to AIDS, specifically for promotion of chemical design strategies and methodologies. A limited number of research projects in the latter area will be supported by the NIGMS in FY 1990.

National Institute of General Medical Sciences

Cellular and Molecular Basis of Disease

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$193,904,000	$204,561,000	+$10,657,000

Purpose and Method of Operation

The Cellular and Molecular Basis of Disease (CMBD) Program provides support for basic biomedical research designed to develop an in-depth knowledge of the structure and function of both the individual cell (the smallest unit of life) and the various "molecular machines" involved in its operation. The latter include the various organelles that are the cell's microscopic components, as well as proteins, carbohydrates, and lipids (fats), and complexes composed of these substances. Because disease occurs when cells fail to perform their myriad life-sustaining tasks with the required degree of precision, the knowledge gained from the studies supported by this program is of vital importance to the research missions of literally all NIH components. Indeed, as noted in an article which appeared in the Washington Post last year, "Cancer and the common cold, heart disease and hay fever, even AIDS and arthritis--all afflict people because of failed mechanisms within cells."

The human body is estimated to contain as many as 100 trillion cells, each of which--for example, the cells in the heart, the pancreas, and the liver--play a very specialized role. Research teams supported by the CMBD Program are using a wide variety of highly sophisticated instruments and techniques to probe every nook and cranny of these cells, seeking to understand not only how they work and interact, but also the consequences of any defects and errors in their makeup or functioning.

One of the most important research topics being addressed by CMBD grantees is the way in which cells communicate with one another. For, as noted in a recent report issued by the National Research Council of the National Academy of Sciences, entitled Opportunities in Biology, research in this area is ".. of special relevance to medicine," since cell-to-cell communication plays a critical role in the regulation of cell functions and "many disease conditions, including cancer and certain types of mental illness, are believed to result directly from abnormal cellular regulation". The report also notes that "research in cellular structure, function and communication should provide a deeper understanding of human disease and probably result in improved treatments or even cures". This is especially true for diseases, such as atherosclerosis (which causes heart attacks and strokes), that result from a complex interaction of several different kinds of cells.

Typical of the research being conducted by grantees of the CMBD Program are investigations designed both to identify the ways in which signals are carried to cells by hormones and other biochemical "message carriers," and to determine how such messages are received and transmitted to the interior of the cell by the signal "receptors" located on the surface membranes of the target cells. Understanding the geography of such cell surface receptors is essential to elucidating their role in selectively accepting and transporting signals received from other locations in the body. Illustrating this is the work of Dr. Peter Walter at the University of California, San Francisco, who received the prestigious Eli Lilly and Company Research Award in 1988, for his success in explaining some of the mechanisms by which proteins are targeted to specific membranous compartments of the cell.

A second important area of research involves "cell cycle control," the study of the biochemical mechanisms that govern cell division, which is, without question, one of the most critical events in the life of a cell. During the past year, NIGMS grantees have made major strides toward developing a clearer understanding of the sequence of steps that result in the division of cells. One of the most dramatic successes in this regard is the purification of a substance called "maturation promotion factor" or MPF, and the biochemical and functional characterization of its two major component proteins. Researchers are now seeking to determine how these two proteins interact to regulate the normal progression of the cell cycle, as well as the way in which flaws in this progression might occur and thus lead to uncontrolled cell division and resultant tumors.

Other important discoveries recently made by CMBD grantees include the following:

- A grantee at Brandeis University has developed detailed information on the activity of a chemical called ethylthioribose. He has shown that this substance is toxic for microorganisms, but not for vertebrate animals, suggesting its possible future use in the development of new antimicrobial agents. Indeed, it is already known that ethylthioribose is toxic to the malarial parasite, as well as a number of other protozoa, which have been notoriously difficult to treat.

- An observation made by a grantee at the Scripps Clinic in La Jolla California, who was studying the production of a chemical substance in the body called adenosine deaminase (ADA), has resulted in a new approach to the treatment of chronic lymphatic leukemia.

- Research by a scientist at Case Western Reserve University in Ohio has provided important new information on the structure and functioning of the mannose-6-phosphate receptor molecules. This has proven useful in the development of a potential new treatment for Gaucher's disease, a rare and often fatal inherited disorder, which causes the spleen to enlarge to the size of a basketball and distorts bone growth and development.

- A scientist at the University of Illinois at Urbana-Champaign has been studying the function of an enzyme called "proline permease" in the transport and binding of lithium, a chemical widely used in the treatment of the manic phase of manic-depressive disorders. His findings are having a sudden and dramatic impact in the field of neuropharmacology, and he presently is seeking to determine the clinical importance of proline permease in helping to both predict treatment failure and to provide insights into the mechanisms by which lithium tolerance and toxicity develop.

- Research performed by an investigator at the University of California, Berkeley, who was working on the transport of urea, resulted in the identification of a flaw on the short arm of chromosome 7 which is associated with problems of urea transport. Interestingly, this same genetic site has previously been associated with certain types of diabetes mellitus, with a rare form of anemia, and with a poorly understood disorder, chronic granulomatous disease.

Support under this program is provided through the use of investigator-initiated research project grants, research center grants, research contracts, and both individual and institutional fellowship awards.

Rationale for the Budget Request

The 1991 request of $204,561,000 for the Cellular and Molecular Basis of Disease Program represents an increase of $10,657,000 over the 1990 estimate. The request will provide for 1,041 research project grants, 67 other research awards, 904 trainees, and one research and development contract.

The CMBD Program will support research in a number of promising areas in 1991, including the following:

Addressins

Research investigators have discovered that, just as the Postal Service uses zipcodes to identify the delivery points for letters, the body uses biochemical labels to assure the delivery of both cells and various chemical substances to organs and tissues where they are needed. This labelling process is usually life-sustaining--in helping monocytes and neutrophils reach sites of inflammation to aid in the healing process, for example--but, when it malfunctions, it also is involved in various pathologies, including the spread of tumors to distant organs. Within the past year, an NIGMS grantee at Stanford University reported the existence of a previously unknown set of substances, which he calls "the addressins," that appear to be responsible for targeting disease-fighting lymphocytes to specific tissues. Further research on the mechanisms of action used by "the addressins" could play a dramatic role in helping researchers better understand the molecular basis for health problems ranging from diabetes to inflammatory disorders to the spread of certain forms of cancer.

Immunogenetics

Working in part with support provided by the CMBD Program, researchers at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts have recently discovered a gene, termed the recombination activating gene (RAG-1), which is believed to be the "master controller" of the body's disease-fighting immune system. The discovery of the RAG-1 gene provides a momentous breakthrough in long standing attempts to understand how the immune system can recognize and coordinate the attack against a vast array of foreign invaders. Scientists believe that further research on the way in which this gene operates will yield dramatic new information on the formation of antibodies, the body's infection-fighting infantry, and perhaps open up new opportunities for exploring the mechanisms involved in disorders of the immune system.

Dynein

Researchers at the Worcester Foundation in Shrewsbury, Massachusetts discovered that a protein which they had previously discovered in brain cells is the same one long recognized to power the tails of sperm cells. These investigators now believe that this protein, called dynein, might be responsible for the motion associated with the mitotic process by which cells divide, as well as for the movement of chemicals within brain cells. More information is needed to determine the precise role that dynein plays in the proper functioning of the brain.

Ion Channel Studies

Ion channels are tunnels that exist in the outer membranes of cells, which serve to selectively permit the movement of electrically charged particles or ions into and out of cells. Such ions--calcium, sodium, and potassium ions, for instance--play a vital role in a wide range of cellular activities including, in humans, functions essential to smell, taste, hearing, and vision, and the action of smooth muscle networks, as well as responses to, hormones and neurotransmitters. NIGMS-supported researchers have made impressive strides, over the past year, in learning how the mechanical "gates" of ion channels operate--how they open and close in response to varying osmotic (water) pressure in their environment, for example. Despite this progress, however, much remains to be learned about both the normal and abnormal (disease-producing) activity of the 60 different types of ion channels discovered thus far.

National Institute of General Medical Sciences

Genetics

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$208,600,000	$214,880,000	+$6,280,000

Purpose and Method of Operation

The Genetics Program supports basic research concerned with elucidating fundamental structures (e.g. genes, chromosomes, nucleic acids, and proteins) and mechanisms involved in inheritance. Inheritance is the process that determines not only the hair or eye color of an individual, but also the individual's capacity to produce those hormones, enzymes, and proteins necessary for a normal, healthy life. Defects in the structure or function of genes are responsible for over 4,000 human disorders, ranging from afflictions such as Down Syndrome and sickle cell disease to lesser known disorders such as pseudohypoparathyroidism, type I, which is characterized by mental retardation.

The primary causes of inherited disorders are "spelling errors" in the long sequences of the four nucleic acids that make up the estimated 100,000 human genes. Just one misplaced nucleic acid in the middle of a sequence of several thousand units can result in a garbled message being sent to the cell's protein manufacturing centers, which in turn can lead either to the failure to produce necessary proteins or to the production of proteins incapable of performing their essential life-sustaining tasks. In cystic fibrosis, for example, a defective gene renders certain proteins incapable of assisting in the movement of chloride and sodium ions across the ephithelial cells of the lungs and pancreas. Because sodium and chloride ions then do not exit normally from these cells, a thick mucus forms leading to chronic bacterial infections that eventually destroy the lungs and pancreas. The impact of cystic fibrosis and other devastating genetic diseases on the Nation's health care system is enormous.

At the present time, remarkably little can be done to remedy genetic defects once they occur. In the last several years, however, there has been a steady progression of new knowledge about the underlying causes of many genetic disorders. Researchers now know the chromosomal locations of nearly 1700 different genes, 700 more than were known in 1987. Included in this body of knowledge is the location of the defective gene on chromosome 6 that contributes to an individual's susceptibility to insulin-dependent diabetes; the defective gene on chromosome 3 responsible for von Hippel-Lindau disease, which causes a form of renal cancer; and the gene on chromosome 2 responsible for the formation of aneurysms (dilated sacs) in certain arteries.

Knowing the chromosome location, the next step is to identify the gene itself so that sequence errors in the flawed genes can be identified. From this information, researchers hope to develop effective methods of diagnosis like those already available for sickle cell disease and a few other genetic disorders. In the long range, however, scientists are seeking to develop the knowledge required to develop effective methods for replacing or repairing defective genes.

NIGMS grantees have played a vital role in the cascade of discoveries in genetics in recent years. Their development of new tools, new concepts, and new information has been derived from basic research studies--usually not targeted to specific disease problems when begun. The critical importance of such research was highlighted in a September 1989 editorial in Science, which stated:

> "the cystic fibrosis gene story . . . explains why scientists believe in the importance of basic research. The tools that made this finding possible arose from a background of basic research into such apparently esoteric and academic subjects as the understanding of the genetic code, the recognition that enzymes from soil bacteria are able to cut DNA (nucleic acids) at specific locations, a solid familiarity with the structure of chromosomes, classical genetics, and statistical probability. Much of the early basic research did not seem relevant to the cystic fibrosis problem, and was pursued in the quest for extended knowledge, not practical application."

A particularly exciting example of the basic research being supported by the NIGMS Genetics Program is the work of Drs. Thomas Cech of the University of Colorado and Sidney Altman of Yale University, joint recipients of the 1989 Nobel Prize in Chemistry. These investigators, after years of painstaking research on the role of the biochemical substance, RNA (ribonucleic acid), made the startling discovery that some RNA molecules (which carry messages from genes to protein manufacturing sites) also act as biochemical catalysts or enzymes capable of breaking large RNA molecules into smaller units. These "catalyst" RNA molecules are known as "ribozymes." Because many viruses, including those involved in cancer and AIDS, are known to carry their genes in the form of RNA, it is possible that ribozymes can be used to attack and destroy such disease-causing viruses. Since the initial discovery by Cech and Altman, nearly 100 ribozymes have been discovered, creating, as the Swedish Academy of Sciences noted, important new tools for genetic engineering and biotechnology, as well as powerful new weapons in the fight against viral infections.

Other important discoveries made by grantees of the Genetics Program help confirm the observation made by Nobelist David Baltimore (Discover, October 1989), that basic research in genetics research can be expected to have a profound effect on studies of cancer:

- Basic researchers at the Salk Institute for Biological Studies in La Jolla, California have identified a previously unknown method by which gene defects can lead to cancer. This discovery could result in improved techniques for early diagnosis of certain forms of cancer. Previously, it was believed that malignant tumors developed only when both copies of an individual's normal tumor-resistant genes were lost or had become ineffective due to a mutation or alteration. These new findings, however, suggest that there is a class of genes capable of inactivating the normal genes that can resist cancer. These cancer-causing genes, or oncogenes, referred to as "v-erbA," are thought to be an aberrant form of a normal gene which is responsible for producing protein receptors for the thyroid hormone. Studies are continuing to elucidate this unusual relationship between normal and abnormal genes.

- Genetics researchers at the University of California, Berkeley recently identified a biochemical mechanism through which high cholesterol levels can trigger tumor formation in the pancreas, colon, and rectum. Working with yeast cells, the investigators showed that the cancer-causing protein produced by the "ras" oncogenes cannot function properly in the presence of drugs that block cholesterol synthesis. This is due to the fact that the "ras protein" requires high levels of cholesterol in order to bind to the host cell. Studies are underway to explore the role of diet in tumor formation and prevention.

- Scientists at the University of Minnesota used a technique called "scanning tunneling microscopy" or STM to produce, for the first time, high resolution pictures of DNA molecules, the basic material of human inheritance. It is believed that such high quality pictures will allow researchers to observe directly the way in which DNA interacts with other biological materials, thereby providing insight into the development of birth defects and cancers when such interactions go awry.

- Using GenBank, the nucleic acid data bank supported by the NIGMS, an NIGMS grantee at the Johns Hopkins University discovered a remarkable similarity between the abnormal wing disc (awd) gene of the fruitflies he was studying and a gene in humans associated with both breast cancer and malignant melanoma. This discovery has provided new insights into the process of tumor spread or metastasis and could result in new treatments for these diseases.

Support under the Genetics Program is provided through investigator-initiated research project grants, research center grants, research contracts, and both individual and institutional fellowship awards.

Rationale for the Budget Request

The 1991 request of $214,880,000 for the Genetics Program represents an increase of $6,280,000 over the 1990 estimate. The request will provide for 1,000 research project grants, 13 other research awards, 600 trainees, and three research and development contracts.

The Genetics Program will support research in a number of promising areas in 1991, including the following:

Gene Therapy

Because of the inadequacy of currently available treatments for genetic diseases, genetic researchers are hard at work to develop new therapeutic approaches geared to directly attacking defective genes, rather than the abnormal proteins generated by those genes. According to a report in Science (June 1989), "Recent results with several target organs and gene transfer techniques have led to broad medical and scientific acceptance of the feasibility of this 'gene therapy' concept for disorders of the bone marrow, liver, central nervous system; some kinds of cancer; and deficiencies of circulating enzymes, hormones, and coagulation factors." NIGMS grantees can be expected to be major contributors to research in this area, designed to overcome the many significant barriers that remain.

Gene Regulation

Genes do not continuously send messages that signal the body to produce proteins. Rather, genes trigger the manufacture of proteins on an "as needed basis." The failure of genes to "turn on or off" at the right moment, however, can mean dysfunction, and result in disease and death, because of a scarcity or an oversupply of particular substances in the body. For this reason, researchers are seeking to identify the mechanisms that regulate gene activation. One of the most promising areas of research, in this regard, involves "heat shock genes" which protect the body against heat and stress by activating themselves to produce certain proteins while, at the same time, turning off the production of other proteins. It is believed that research on heat shock genes will result in significant new information on the regulation of all genes.

Effect of Steroid Hormones on Gene Transcription

NIGMS grantees have recently discovered a family of steroid hormone receptors that influence the way in which genetic messages are decoded by protein manufacturing centers in the body. Research on these and other chemicals that affect the reliability and reproducibility of the interpretation of the genetic messages is vital to an understanding of the development of disease and to its ultimate prevention.

RNA Splicing

Virtually all human genes contain extra internal DNA sequences that do not code for (trigger the manufacture of) the gene's protein product. As an essential step for gene expression, these sequences, called "introns," are removed from the messenger RNA transcript of the genes by a process called "splicing." It is not yet understood, however, how the correct sites for splicing of the messenger RNA are recognized. Several genetic diseases result from mutations that cause errors in RNA splicing. For example, many thalassemias (genetic defects in hemoglobin) are due to mutations that cause incorrect or inefficient messenger RNA splicing. Also, alternative splice sites are sometimes used to generate different protein products from a single gene sequence. For example, the RNA transcript of the gene for the hormone, calcitonin, is spliced differently in the thyroid and in the hypothalamus to produce two different peptide hormones. It is important to understand both the mechanism by which mutations result in faulty splicing and the way in which the cell normally regulates the choice between alternative splice sites. NIGMS grantees are actively pursuing research to address these questions.

Pattern Formation Genes in Development

Birth defects account for 20 percent of the deaths in babies one year old or younger. Some of these birth defects are thought to be due to abnormalities in genes that act very early in development to establish the embryo's general body plan. Fruitflies serve as excellent models for studies of development in higher organisms, including humans. In fruitflies, these genes act in a hierarchical manner to specify, in increasing detail, the various structures of the embryo. Scientists in a number of laboratories are investigating the interrelationships of pattern-formation genes that act early in the development of fruitflies and how abnormalities in these genes cause defects in the adult flies.

National Institute of General Medical Sciences

Pharmacological Sciences Program

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$99,155,000	$103,478,000	+$4,323,000

Purpose and Method of Operation

The Pharmacological Sciences (PS) Program supports research and research training in three areas: pharmacology, anesthesiology, and bio-related chemistry. The research grant portfolio in pharmacology covers a spectrum of studies from the most basic, such as the molecular pharmacology of cell receptors, to the clinical, for example, the basis for variability in individual response to drugs. One area of growing activity is the use of the tools of biophysics and modern molecular biology to determine the structure of macromolecules of pharmacological interest, such as the structure of a particular protein that serves as the site of a drug's action at the cellular level. In the area of anesthesiology, research also ranges from the basic to the clinical, with increasing interest in studies to identify the specific sites of anesthetic action. Thus, the chemical and physical structure of the receptor proteins to which certain anesthetics bind, and the tissue-specific regions upon which particular anesthetics act are being explored. The third area supported by the PS Program is bio-related chemistry. Advances in research instrumentation and techniques, including the exploitation of computer modeling, are greatly expanding the frontiers of studies in basic chemistry. Inventive approaches in this area are helping to identify natural plant and animal products of potential therapeutic use in humans, developing synthetic approaches to the design of new drugs and drug delivery methods, and discovering the intricacies of the myriad of chemical reactions that are part of normal physiology, or are altered by a disease process.

While the rich array of research in all three of these areas is yielding important results, one line of study--research on the so-called "G-protein pathway"--has received heightened attention recently, due, in part, to the selection of Dr. Alfred G. Gilman of the University of Texas Southwestern Medical Center at Dallas to receive the prestigious 1989 Albert Lasker Basic Research Award. Dr. Gilman, an eminent pharmacologist, discovered G-proteins about 10 years ago. Since then, he and numerous other scientists have been exploring the structure and function of the components of the G-protein pathway, which is one of two primary means of communication between cells. The G-proteins are the link between cell surface receptors (the sites targeted by hormones, signal proteins, and drugs) and the messenger system inside the cell which initiates the intended effect of such external agents. Thus, the G-protein pathway must work properly for our bodies to function in a healthy manner.

Some interesting recent findings by Dr. Gilman and others are expanding our understanding of this pathway, while at the same time raising intriguing new questions. Dr. Gilman has examined the enzyme adenylyl cyclase, which plays a key role in converting the "messages" transmitted via the G-protein pathway to so-called "second messenger" molecules that carry the instructions within the cell to the appropriate active site. By determining the protein sequence of adenylyl cyclase, and through other analyses of its structure, Dr. Gilman has discovered that this enzyme may play a role in cross-membrane transport (transport of important molecules across the cell surface). Its structural similarity to ion channels, the other primary pathway for moving external signal molecules into the cell, suggests that this key enzyme in the G-protein pathway may be of much more significance than previously supposed.

Another significant line of inquiry involving G-proteins is being pursued by Dr. Henry Bourne at the University of California, San Francisco. His laboratory has been exploring the role of a specific G-protein, G_{as}, in the growth of pituitary gland tumors. He has found that a mutation of the normal cellular oncogene, whose protein product is this G_{as} protein, alters the structure and function of the protein in such a way as to "turn on" a message to the pituitary cells to continue to grow. Normally, the G_{as} protein, like other G-proteins, is inactivated as part of a cyclical process. However, in this case, inactivation of the G_{as} protein does not occur, leading to the uncontrolled production of growth hormone, which results in growth of the tumor. Interestingly, the protein product of one of the best understood oncogenes, ras, appears to share some similarities in structure and function with the G_{as} protein. Clearly, this line of scientific research warrants further investigation, due to its potential relevance to the cellular transformation that occurs in the formation of tumors, particularly malignant tumors.

Another line of exploration of the family of G-proteins is being undertaken by Dr. Eva Neer at the Brigham and Women's Hospital in Boston. Her research involves examining the structure and function of each of the three structural subunits of the G-proteins, the α, β, and Γ. The structure of the α subunit varies and appears to be the most influential in determining the role of the particular G-protein in transmitting hormonal and other signals across the cell membrane. However, the β and Γ subunits, whose structures are not so variable, and whose role in the process of carrying signals across the cell membrane was previously thought to be minor, now appear to play a larger role. Dr. Neer has found that the β and Γ subunits, in fact, mediate the opening of certain channels in the cell membrane that permit the flow of chemical messengers into the cell. Improving our understanding of this phenomenon may help scientists develop drugs that take advantage of this G-protein pathway to correct abnormal cellular functions, such as those that typify whooping cough, travelers' diarrhea, and cholera.

Other noteworthy accomplishments made by grantees of the Pharmacological Sciences Program over the past year include the following:

- An excellent example of basic research moving toward significant clinical application is work being done in a laboratory at Bowling Green State University. A combination of light, oxygen, and certain chemical agents is being developed as a cancer therapy. The process involves using light to excite chemical compounds called photosensitizers, which, in turn, transmit their excess energy to oxygen molecules. These oxygen molecules become highly reactive and destroy diseased tissue. This research is now concentrating on identifying appropriate combinations of light at specific wavelengths and photosensitizing compounds that will permit selective targeting of cancer cells for destruction.

- A grantee at the State University of New York, Stony Brook, has discovered two toxins, termed "latrunculins" after the sponge from which they are derived. These toxins show promise as tools for studying the role of the protein, actin, in nonmuscle cells. Actin is an abundant protein which plays a key role both in muscle movement and in a number of vital cellular processes, such as growth and differentiation, in nonmuscle cells. Studying actin's role in nonmuscle cells has been particularly difficult. The latrunculins, however, inhibit the activity of actin in nonmuscle cells, facilitating the study of actin's role in maintaining cell shape, in cell division, and in other cellular processes.

- A long time grantee and MERIT award recipient at Colorado State University has isolated a new, apparently non-toxic agent for dissolving blood clots from the venom of the western diamondback rattlesnake. Early tests of this thrombolytic agent in rats indicate that it might hold promise as a therapeutic agent for administration to humans.

Support under this program is provided through the use of investigator-initiated research project grants, research center grants, research contracts, and both individual and institutional fellowship awards, including those awarded under the biotechnology training program.

Rationale for the Budget Request

The 1991 request of $103,478,000 for the Pharmacological Sciences Program represents an increase of $4,323,000 over the 1990 estimate. The request will provide for 520 research project grants, 3 research center grants, 2 other research awards, 516 trainees, and 1 research and develoment contract.

In 1991, the Pharmacological Sciences Program will support research in a number of promising areas, including the following:

Immunopharmacology

Interest in this field of pharmacology has grown as the utility--and side effects--of immunosuppressant drugs, such as cyclosporine A, have become widely recognized. Cyclosporine A has been used to prevent organ rejection after transplantation and to treat certain autoimmune and inflammatory disorders, such as rheumatoid arthritis and psoriasis. However, its use produces some serious toxic side effects to the central nervous system, kidneys, and liver. A number of grantees of the PS Program are examining the molecular structures of cyclosporine and other immunosuppressants to determine which portions of their structures account for their toxic effects. Others are examining the nature of each toxic phenomenon to determine which step(s) in the toxic reactions might be susceptible to inhibition. This research may yield information useful in designing new immunosuppressant agents, the toxic effects of which are minimized or eliminated.

Anesthesiology

Increasingly, research in this field is moving toward examining the activity of anesthetics at the molecular level. Much of this work is aimed at determining just how and where the anesthetic molecules exert their effects in the body. Scientists at Stanford University, for example, have uncovered the first evidence that a specific set of receptors in brain tissue cause general anesthetics to induce sleep. Other researchers at the University of Minnesota are looking for the molecular basis of malignant hyperthermia. This is a genetic defect that triggers potentially fatal temperature elevation and muscle rigidity when general anesthetics are administered to those affected. This research has produced the first evidence that, in those susceptible to malignant hyperthermia, a specific intracellular calcium channel becomes overactive, releasing too much calcium and leading to the muscle rigidity characteristic of this disorder. Studies such as these are opening up new opportunities to define the molecular basis of anesthetic action.

Drug Delivery

Grantees are attempting to design new or improved methods for targeting drugs with optimum specificity to the sites where their therapeutic activity must occur. One approach being explored proposes to create tiny artificial liposomes, or "membrane sacks," that contain drugs. The composition and shape of these "sacks" are being tailored to permit them to seek out and bind to specific sites. A project of this type is underway at Emory University. Scientists there have designed "membrane sacks" that are somewhat porous, allowing the slow release of the contents at the desired location. Such a drug delivery system might be useful in treating some disorders, in which slow release of medication over a period of time would be of greater therapeutic benefit than the concentrated effects of taking frequent, larger doses. Creative approaches to designing new drug delivery systems should make it possible to enhance drug efficacy and minimize side effects in the future.

Novel Approaches to Synthesis of Anti-viral Agents

In many laboratories supported by the PS Program, research is underway to develop new, more effective anti-viral agents. Some scientists are focusing on how to inhibit viral activity by interfering with some portion of the complex viral replication process. For example, the approach of researchers at the University of Kansas is to attempt to manipulate the structure of a particular viral enzyme which catalyzes one key step in the viral replication process. This laboratory is using computer modeling and site-directed mutagenesis to determine the structure of the enzyme, since its crystal structure is not known, and to deduce its active site. Part of their approach involves inferring the structure of this enzyme by comparing it to one that is almost identical in composition and for which the crystal structure is known. Once the structure of the enzyme is clear, scientists may be able to design drugs that will inactivate it, thus interfering with viral replication. Another PS

Program grantee at Northwestern University is exploring why some nucleic acid analogs, called oligonucleotides, to which a cholesterol-related compound is attached, demonstrate enhanced antiviral activity, and are more successful at blocking viral replication than the oligonucleotides alone. While the cholesteryl compound was originally attached to the oligonucleotides to facilitate their transport across the cell membrane, the unexpected benefit of heightened antiviral activity opens new areas for fruitful research, and may eventually lead to the development of new antiviral drugs.

National Institute of General Medical Sciences

Biophysics and Physiological Sciences

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$144,533,000	$151,821,000	+$7,288,000

Purpose and Method of Operation

As its title suggests, the biomedical research and research training supported by the Biophysics and Physiological Sciences (BPS) Program, is diverse and heterogeneous. It ranges from studies of the structure of DNA and proteins to development of research instrumentation, and examination of the body's responses to trauma, particularly burn injury. Thus, the results of the work supported by the BPS Program impact broadly across many research disciplines. This is particularly true in the structural biology area, where the approaches and conclusions of the scientists who are attempting to determine the "architecture" of important macromolecules, such as DNA and proteins, are changing the way in which other scientists tackle knotty research problems. For example, researchers are applying the techniques of structural biology to design more effective drugs. This is done, usually using sophisticated computer modeling, by figuring out which structural elements of potential drug molecules would best "fit" within the crevices of the structure of the target site, often a receptor molecule. This same approach, as well as variations of it, are also helping cellular and molecular biologists to understand the structural basis for the normal interactions of the many molecules involved in the thousands of physiological processes which maintain the normal functioning of the body.

One important area in which studies of structural biology are being conducted is the structural basis for the interaction between regulatory proteins and DNA. Scientists are attempting to determine which structural units or domains of the regulatory proteins must link to a segment of the DNA in order to bind to it and "turn on" or "turn off" the expression of genes. To date, at least two structural motifs have been identified that appear to be at work in the binding process. These are structural domains which are common in many regulatory proteins and which govern how and where the proteins bind to the DNA. One of these is called the "helix-turn-helix" motif. Dr. Paul Sigler at Yale University is studying an important example of this motif at work. He has determined that the active binding domain of a particular protein, termed the "trp-repressor", fits the helix-turn-helix motif, twisting and twisting on itself. Equally importantly, he has elucidated the conformational change that the protein undergoes during the binding process as it goes from its unbound to its bound state. Because this trp-repressor protein regulates the gene responsible for encoding the message for the production of tryptophan, one of responsible for encoding the message for the production of tryptophan, one of the amino acid building blocks of many proteins, this is a significant discovery.

Recently, Dr. Peter Wright of the Scripps Clinic has described a second structural motif, termed the "zinc-finger" motif, found at the active DNA-binding site of certain regulatory proteins. Because the particular peptide he is studying has not yet yielded to X-ray crystallographic analysis, (the most common tool for structural biologists), Dr Wright chose, instead, to approach its study by using 2-dimensional nuclear magnetic resonance (NMR) imaging to elucidate the peptide's structure. He has discovered that a particular region of the peptide forms a unique finger-like conformation in the presence of zinc which allows it to bind to DNA. Dr. Wright's work is now aimed at refining the structural analysis of the bound DNA-zinc finger complex.

Continued study of the structural features of macromolecules, such as proteins, will prove important, not only to understanding genetic and other subcellular processes crucial to health, but also to the production of important biological products by the biotechnology industry. Many biotechnology firms are attempting to synthesize pharmaceuticals and other biological agents that depend on specific structures in order to function properly. Before these firms can manufacture and market such macromolecules, however, it will be critical to expand our understanding of the structural basis for both the stability and the activity of the molecules.

Other noteworthy recent accomplishments by researchers supported by the BPS Program include the following:

- A grantee at Yale University has developed a novel adaptation of a technique commonly used to detect the presence of, and to determine the composition of, minute amounts of chemical compounds. The standard technique uses mass spectroscopy, usually in conjunction with gas or liquid chromatography, to make definitive analyses. In order to adapt this technique to the identification of the sequences of fragments of proteins, it was necessary to devise a method to "vaporize" the proteins prior to analysis, normally a difficult task. By subjecting a minute sample of a protein to an electrospray, it is possible to use this technique as the first step in a process that ultimately allows scientists to sequence both the amino acids of the protein and the DNA of the gene that codes for the protein. Further development of this new technique has important implications for the Human Genome Project, one goal of which is to sequence the entire genome of man and of certain other model organisms.

- Grantees at the University of Oregon and at Johns Hopkins University have begun to build a library of information documenting the correlations between the structural stability of various proteins and the presence or absence of, or the rearrangement of, their amino acid components. Understanding the structural forces that govern protein stability is essential to the biotechnology industry because genetically engineered therapeutic products, such as human interferon, human insulin, and tissue plasminogen activator (TPA), can only be produced and marketed if their stability, over time, is assured.

- A grantee at Wayne State University has determined the three-dimensional structure of thrombin, the central enzyme in the regulation of blood-clotting. Thrombin is often termed a "killer enzyme" because of its role in uncontrolled clotting, a phenomenon that contributes to approximately 40% of all deaths. Knowing the structure of this enzyme should help researchers design an effective inhibitor of its activity, so that the blood clotting process can be more effectively controlled, preventing excessive bleeding when necessary and keeping arteries unclogged, when appropriate.

- Grantees at the Scripps Clinic and at Cornell University Medical Center have determined that the protein called tumor necrosis factor (TNF) is a significant contributor to the process that leads to organ failure, and often death, in patients suffering from shock induced by severe bacterial infection. They are doing basic laboratory studies to explore how the gene that codes for TNF gets "switched on," so as to overproduce this protein in the face of infection. In addition, they and others are performing clinical trials in which antibodies to TNF are administered to patients suffering from this type of shock. These trials suggest that the antibodies can prevent the organ failure seen in septic shock.

Support under this program is provided through the use of investigator-initiated research project grants, research center grants, research contracts, and both individual and institutional fellowship awards.

Rationale for the Budget Request

The 1991 budget request of $151,821,000 for the Biophysics and Physiological Sciences Program represents an increase of $7,288,000 over the 1990 estimate. This request will provide for 639 research project grants, 6 research center grants, 21 other research awards, 1,275 trainees, and 2 research and development contracts.

In 1991, the BPS Program will give special emphasis to the following program areas:

Protein Structure

While modest progress has been made in attempts to determine the complex structures of proteins, still remaining is the two-fold challenge of understanding how proteins "fold" into the shapes that permit them to function properly, and of identifying the shapes assumed by the thousands of proteins at work in the body. These challenges are all the more difficult because it appears that a protein's shape is dynamic, changing with varying physiological conditions and with the particular function being performed. Researchers performing structural studies are increasingly supplementing the traditional use of X-ray crystallography with 2-dimensional nuclear magnetic resonance, since, using this technique, the proteins under study need not be laboriously crystallized prior to analysis. Another perspective on the structure of proteins is gained from the use of a technique called "site-directed mutagenesis," which selectively alters the amino-acid components of a particular protein. The effects of such changes on the structure and function of the protein are then analyzed.

Nucleic Acid Structure

In recent years, scientists have learned that DNA, the long strand of genetic material that provides the fundamental set of instructions for growth and all other life processes, has a dynamic shape. It is clear from recent research that, at times, the tightly coiled DNA helix bends and untwists in localized areas when it is "engaged" in certain functions, such as linking to the proteins that regulate gene expression. Further research into this phenomenon promises to tell us a good deal about how the dynamic structure of DNA, as well as of the RNA family of nucleic acids, determines or reflects function.

Instrumentation Development

A number of NIGMS grantees continue to develop new or enhanced instrumentation for biological research. This work ranges from adapting such tools as ultrasound to new applications, to improving the speed or precision of commonly used instrumentation, such as chromotographic equipment, so that smaller and/or less pure samples of biological material can be analyzed at faster rates. Since modern molecular biology is heavily dependent on sophisticated instrumentation, and since such instrumentation can frequently reduce otherwise labor-intensive laboratory tasks to more routine, automated work, the pay-off of such instrument development can be substantial.

Trauma and Burn Research

Research on trauma, including burn injury, will continue to be directed to improving our understanding, at the molecular, cellular, and physiological levels, of the complex reactions that occur following severe trauma. Studies will explore such areas as septic shock, injury-induced alteration of metabolism and the immune response, heat shock proteins and other factors involved in wound healing and multiple organ failure. Advances produced by these studies will help reduce the morbidity and mortality resulting from trauma and burn injury.

National Institute of General Medical Sciences

Minority Biomedical Research Support

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$29,794,000	$32,326,000	+$2,532,000

Purpose and Method of Operation

The Minority Biomedical Research Support (MBRS) Program was transferred from the Division of Research Resources (DRR) to the NIGMS at the start of FY 1990. As a result, NIGMS now administers the two largest NIH programs providing support to minority research institutions (MBRS and the Minority Access to Research Careers Program). The goal of the MBRS Program is to increase the representation in biomedical research of underrepresented ethnic minority groups. To accomplish this goal, the Program awards institutional grants to enable faculty and students at minority institutions to participate in biomedical research and related enrichment activities. In addition, the MBRS Program improves the research environment at grantee institutions by providing suitable, up-to-date laboratory equipment and work stations.

The MBRS Program began in 1972 as an effort to strengthen institutional research capabilities and to provide research opportunities to faculty and students at colleges, universities, and health professional schools having substantial enrollments of ethnic minorities. Later, the program was expanded to include two-year institutions with 50 percent or more minority student enrollment, as well as recognized American Indian tribes and Alaskan Native Corporations.

The MBRS Program has grown significantly since its beginning. The number of MBRS grants awarded has tripled since FY 1972; in FY 1989, 98 MBRS awards were funded for a total of $39.4 million. Of this, 28.1 million were DRR funds, and $11.3 million represented cofunding by other NIH components and components of the Alcohol, Drug Abuse, and Mental Health Administration. Of the 98 awards, fifty-six were awarded to institutions that primarily serve Blacks, five to those that primarily serve American Indians, nine to those that primarily serve Puerto Ricans, 11 to those that primarily serve other Hispanics, and two to those that primarily serve Pacific Islanders. The remaining grants were awarded to schools with large, mixed populations of minority students. These funds helped support the research efforts of 753 faculty members on 733 projects, and supported research positions for 1,101 undergraduate and 448 graduate students. In all, approximately 16,000 students have participated in MBRS-sponsored research since the Program began.

Two major grant mechanisms are used to accommodate the diverse resources and needs of eligible institutions. The MBRS Traditional Program, which began in 1972, supports faculty research projects and/or student participation in ongoing biomedical research under the supervision of an established investigator. The MBRS Program for Undergraduate Colleges, which began in 1985, supports required enrichment activities, as well as options for pilot studies or regular research projects. Enrichment activities include workshops, attendance at scientific meetings, and summer research experiences for faculty and students at off-campus laboratories. The MBRS Program for undergraduate colleges is intended to enhance research capabilities at colleges that have not been successful in competing in the MBRS Traditional Program. Thirteen institutions received funding under this mechanism in FY 1989.

In addition to the two major funding mechanisms described above, the Program has established two special supplemental grant initiatives. The MBRS Supplemental Grant for Instrumentation, which was started in FY 1983, provides funds to acquire or upgrade research equipment for use by at least two MBRS faculty members. The MBRS Supplemental Grant for Animal Resource Improvement, which began in FY 1987, provides support for altering or renovating laboratory animal facilities, acquiring relevant equipment, and providing short-term training in the care and use of research animals. Three of these awards were made in FY 1989.

The positive impact of these MBRS programs can be seen in the success stories of numerous grantee institutions that use MBRS support to develop academic programs in the biomedical sciences. Some examples include the following:

- At Selma University, the MBRS Program played a leading role in elevating the university's status from a two-year to a four-year institution and in developing its new Bachelor of Science degree program in biology.

- At Florida A&M University, the MBRS Program was instrumental in the development of programs leading to the Ph.D. and Pharm.D. degrees. Last year, Florida A&M graduated its first doctoral student in the School of Pharmacy.

- At Meharry Medical College, the MBRS Program is credited with the initiation and development of several Ph.D. programs in the biomedical sciences. The majority of Ph.D. students there now receive MBRS support.

- At Atlanta University, the majority of Ph.D. students in the biomedical sciences have been supported by the MBRS Program. To date, this includes 50 Ph.D. graduates, many of whom have been hired as faculty at other minority institutions.

- Prior to 1972, at Winston-Salem State University (which is one of the original MBRS grantee institutions), no graduate had ever gone to medical school or to a graduate program in a basic medical science. Since 1972, the university has graduated 73 MBRS students. Of these, 25 have earned the M.D. degree and eight are in medical school, while 14 have earned graduate science degrees and five are in graduate school. In addition, seven have earned the D.D.S. degree or are in dental school, and one has earned a D.P.M. degree.

- At Montana State University, the MBRS Program has played a key role in enabling the university to provide tribal colleges on seven different reservations with access to scientific research resources. The MBRS Program there is in its fifth year, and 18 bachelor's degrees and one master's degree in the sciences already have been awarded to Native American students. This includes the first Native American female (from Montana) to receive the D.V.M. degree.

Behind each of these institutional success stories, there are numerous individual success stories. One of the most outstanding is that of Erich Jarvis. As a sophomore at New York's Hunter College in 1984, he was accepted into that school's MBRS Program. While in the Program, he worked in the laboratory of Dr. Rivka Rudner and became an exceptional scientific researcher. Mr. Jarvis' work involved the mapping of all ten active genetic units in the genome of the microorganism, *Bacillus subtilis*. He cloned, sequenced, and functionally characterized the regulatory regions of one of the genes, *rrnD*, and has shown it to be involved in chromosomal arrangements. The results of his work were presented in six publications and ten scientific presentations at national and international conferences on genetics. During the 14th Annual MBRS Symposium in 1986, he received the Award for Excellence in undergraduate biomedical research. Mr. Jarvis, who was recruited by many prestigious graduate programs, eventually accepted a predoctoral fellowship at Rockefeller University, where he is now working toward a Ph.D. degree in neurobiology.

Although Erich Jarvis is an outstanding example of a successful MBRS student, his success is by no means uncommon. Preliminary data have indicated that about 400 MBRS students complete the B.S. degree each year, and that over 80 percent of them go on to pursue an advanced degree in the health sciences. The following table shows the percentage of MBRS graduates in each of the last ten years who indicated that they were pursuing advanced health science degrees.

PERCENT OF MBRS GRADUATES PURSUING ADVANCED DEGREES

1979	1980	1981	1982	1983	1984	1985	1986	1987	1988
88	81	85	84	84	74	83	82	76	77

Another highlight of the MBRS Program was the 17th Annual MBRS Symposium held October 5-7, 1989, in Houston. It was attended by 1500 students and faculty conducting biomedical research at colleges and universities throughout the United States and Puerto Rico. The Symposium featured approximately 400 posters and platform presentations by MBRS students, seminars by eminent biomedical researchers, and exhibits by graduate schools, governmental and private agencies, and biomedical research firms. The banquet address was given by Dr. Louis Sullivan, Secretary of the Department of Health and Human Services.

Rationale for the Budget Request

The 1991 request for the MBRS Program is $32,326,000, an increase of $2,532,000 over the 1990 level. This request will support 98 awards, the same number as in 1990.

Co-funding by the categorical institutes of the NIH will continue in 1991. This activity permits cooperating institutes to support projects of direct concern to their stated missions and assists investigators in gaining individual research grant support from the categorical institutes. In 1991, the categorical institutes of the NIH have budgeted $10,719,000 for co-funding support of the MBRS Program, bringing the total funding level by NIH in 1991 to $43,045,000, an increase of $3,423,000 over the 1990 level.

National Institute of General Medical Sciences

Minority Access to Research Careers

Authorization: Indefinite.

Budget Authority:

1990 Appropriation	1991 Estimate	Increase or Decrease
$10,670,000	$13,359,000	+$2,689,000

Purpose and Method of Operation

Over the past year, numerous articles in both the scientific and popular press have warned of an impending serious shortage of scientists in this country. The widely-predicted crisis is rooted in an incontrovertible demographic fact: because of low birthrates in the 1960s and 1970s, the college-age population is shrinking. According to the Census Bureau, the number of 18- to 24-year-olds will decline to under 24 million in the mid-1990s, compared to being over 30 million in 1980. Currently, a little over 5 percent of 22-year-old Americans earn B.S. degrees, and approximately 5 percent of B.S. holders obtain Ph.D. degrees. According to the National Science Foundation, unless those fractions increase, there will be a shortage of 400,000 scientists and 275,000 engineers by the year 2006.

Although the dip in the college-age population will be temporary--the children of the baby boomers will be entering their early 20s in growing numbers in the late 1990s--the Nation could still be faced with a shortage of scientific manpower over the long term because of a growing proportion of non-whites in the population. Current new additions to the workforce are mainly women, blacks, Hispanics, and immigrants, all of whom have traditionally been underrepresented in science and engineering careers. According to the Bureau of Labor Statistics, blacks and Hispanics will account for almost 45% of the total growth of the labor-force over the next decade. During this period, the Bureau also predicts a net increase of more than 13 million female workers, compared with 7.7 million male workers.

In view of these trends, the Congressionally-chartered U.S. Task Force on Women, Minorities, and the Handicapped in Science and Technology estimates that, in order for a shortage of scientific personnel to be avoided, the nation's colleges must graduate, in science and engineering, twice as many white women, five times as many blacks, and seven times as many Hispanics--in every year of the 1990s. The Task Force's projected demand for women and minorities with doctoral degrees in science and engineering is even higher: three times as many white women, 12 times as many Hispanics, and 20 times as many blacks.

Achievement of such dramatic increases would be extremely difficult in any case, but becomes an even more imposing task because of the underrepresentation of women, blacks, and Hispanics in the fields of science and engineering. Currently, only about 25 percent of practicing scientists and about 5 percent of engineers are women. Less than 3 percent of practicing scientists and engineers are minorities (excluding Asian Americans). Nor is the situation significantly improving. In 1988, for example, only 47 black Americans received doctorates in science and only 15 in engineering.

Alleviating this seemingly insurmountable problem, which has its roots in the deeper problems of poverty, discrimination, and educational deficiencies, has been the goal of the NIGMS Minority Access to Research Careers (MARC) Program. The U.S. Task Force on Women, Minorities, and the Handicapped in Science and Technology cited MARC as a "prime example of a successful federal intervention program established to give minorities and women access to science and engineering." Established in 1972, the MARC Program provides special research training opportunities and incentives in the biomedical sciences in order to attract and retain minority students with potential for research careers. Four mechanisms are used to implement this Program. These are: (1) the MARC Honors Undergraduate Research Training Program; (2) the MARC Predoctoral Fellowship Award; (3) the MARC Faculty Fellowship Program; and (4) the MARC Visiting Scientist Award.

The MARC Honors Undergraduate Research Training Program was established in 1977 at the suggestion of the Congress, based on recommendations made by Institute consultants and staff. It emphasizes the value and importance of providing biomedical research training at the undergraduate level. Its objectives are to help minority institutions develop strong undergraduate science curricula, to stimulate an interest among undergraduates in biomedical research, and to increase the number of well-prepared minority students who can compete successfully for entry into graduate programs leading to the Ph.D. degree in the biomedical sciences. Under this program, highly qualified minority institutions receive support for courses and research training for honors undergraduates in their third or fourth year of college, and who plan to obtain the doctorate degree (Ph.D.) in an area of biomedical science. Sixty minority institutions across the country have received support under this program. Of note is the fact that at these institutions the number of students earning biological science degrees has increased while the percentage of all students nationwide (minority and nonminority) earning biological science degrees has decreased.

Eligible students are selected on the basis of both their academic achievements and their commitment to seek graduate training in the area of biomedical science. In 1989, the Honors Undergraduate Program had 165 graduates, bringing the total number of graduates since 1978 to over 1,450. To date, approximately 80 percent of these graduates have gone on to either graduate or professional schools. It is hoped that this program will result in a progressive increase in the pool of qualified minority scientists who are available to compete successfully for research grants and to serve as mentors and role models for new generations of minority biomedical investigators.

The MARC Predoctoral Fellowship Award provides support for outstanding graduates of the MARC Honors Undergraduate Program to pursue doctoral degrees in the biological sciences. Established in 1981, this award mechanism was designed to provide a further incentive to graduates of the Honors Undergraduate Program to obtain research training in the nation's very best graduate programs. Awards are conditional upon acceptance into an approved doctoral (Ph.D.) degree or combined degree (M.D.-Ph.D.) program in the biomedical sciences. To date, 250 applications for this award mechanism have been received, and 127 have been awarded. The relatively low number of applications is regarded positively_--an indication that significant numbers of MARC Honors graduates are successfully entering the educational mainstream and securing their own predoctoral funding from graduate schools anxious to recruit them.

The MARC Faculty Fellowship Program provides opportunities for advanced research training to selected faculty members of four-year colleges, universities, and health professional schools in which student enrollments are drawn substantially from minority groups. These institutions may nominate faculty members for MARC Fellowships in support of a period of advanced study and research training in major graduate departments and laboratories, either as candidates for the Ph.D. degree or as investigators obtaining postdoctoral research training in the biomedical sciences. When the period of training is completed, fellows are expected to return to their sponsoring schools to teach and conduct research. Since its inception in 1972, 225 individuals have received support under this program. Of those who have completed the training period, approximately 90 percent have returned either to their original home institution or to another minority institution. The research training sites have included 80 universities, research laboratories, and federal institutions in 34 states and 5 foreign countries. The home institutions also are broadly representative, including 74 colleges and universities in 25 states and the Commonwealth of Puerto Rico.

The MARC Visiting Scientist Award provides support for outstanding scientist-teachers to serve in the capacity of visiting scientists at four-year colleges, universities, and health professional schools in which student enrollments are drawn substantially from minority groups. The primary intent is to strengthen research and teaching programs in the biomedical sciences for the benefit of the students and faculty at these institutions, by drawing upon the special talents of scientists from other, primarily majority, institutions. Reciprocal benefits also should accrue to the Visiting Scientist through the added experience gained by involvement in innovative science education and developmental research programs. The award includes detailed arrangements for the Visiting Scientist to reside in the campus community and to participate fully in programs of teaching, research development, and counseling. This necessitates considerable advance planning on the part of both the host institution and the prospective visiting scientist. As a result, only 17 applications have been received and 10 awards made since the inception of this award mechanism. However, staff efforts to advertise and encourage applications continue to be made, and both the MARC Review Committee and the National Advisory General Medical Sciences Council strongly support continuation of this award mechanism.

In addition to the above, the MARC Program has sought to provide advice and technical assistance to minority students, colleges, and universities wherever possible, and to encourage discussion regarding the obstacles which continue to hold the number of minority scientists in the country to a relatively low level. In October 1989, the Program sponsored the eighth annual

MARC Scholars Conference for over 800 minority students, graduate faculty, and other attendees. The conference provided a forum for discussion of research experience through oral and poster presentations by the students of the MARC Honors Undergraduate Research Training Program. MARC honors undergraduate students also had an opportunity to discuss the strategies for optimal preparation for graduate school, including identifying and applying for excellent research experiences, preparing for the Graduate Record Exam, determining which graduate schools offer the best and most appropriate programs, and developing sound graduate school applications. At the meeting, scientists, representatives from industrial concerns, government laboratories, and universities had an opportunity to discuss training and education opportunities with these students.

Rationale for the Budget Request

The 1991 request for the MARC Program is $13,359,000 and 711 trainees, an increase of $2,689,000 and 136 trainees over the 1990 estimate.

In FY 1991, as in previous years, the MARC Program will continue to place primary emphasis on its Honors Undergraduate Research Training (HURT) component, with roughly 80 percent of the MARC budget being allocated to this component. It should be noted that, in addition to the success of this activity in terms of its graduates entering doctoral programs, a 1985 Institute of Medicine study found that, of former MARC undergraduate trainees who are no longer in school, 62 percent are employed in science or engineering fields. This is above the levels found in the most closely comparable national data. Another indication of the success of this program is the continued high demand for MARC trainees. At the annual MARC Scholars Conference, trainees are recruited by dozens of major universities. MARC program directors report that they frequently are approached by graduate schools with inquiries about their trainees. There is also competition for MARC honors students among the large number of schools that run summer training programs. Such willingness to invest in the short-term training of these students is seen as a very positive indication of the quality of the trainees. In addition, program directors report that companies in the biomedical research industry have a strong interest in MARC honors students.

The "honors" concept of the MARC Program has encouraged institutions that are recipients of awards to establish a different and more rigorous program for students in the basic sciences. Many have incorporated an honors thesis requirement for graduating MARC students. The provision of funds for seminars and lectures, release time for faculty members, up-to-date equipment and supplies, as well as the addition of full-time and part-time faculty in disciplines not formerly represented, have all contributed to academic enrichment. In addition, specialized courses have been set up to prepare students to take standardized tests--an area in which minority students traditionally have been weak. The scientific activities of grantee departments have been strengthened and, as a result, it has become more common for MARC faculty members and trainees to be invited to present papers at local, regional, and national scientific meetings. We are also beginning to see a larger number of students serving as coauthors of scientific papers. The fact that MARC students are performing well in graduate school has provided an increased number of role models for minority students, and has resulted in a significant increase in the number of science majors at minority institutions having MARC awards. For example, a MARC undergraduate was recently named American Indian Student of the Year by the National Indian Education Association. In summary, the MARC Program, and especially its Honors Undergraduate Research Training component, has produced a new awareness among minorities of the opportunities available in biomedical research, and has provided the means to take advantage of these opportunities.

National Institute of General Medical Sciences

Intramural Research

Authorization: Indefinite.

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
22	$1,052,000	22	$1,099,000	--	+$47,000

Purpose and Method of Operation

The NIGMS has a small, but unique, intramural research program formally known as the Pharmacology Research Associate Training (PRAT) Program. Under its auspices, each year, a group of young scientists is selected for a two-year period of postdoctoral research experience under the tutelage of preceptors in the laboratories of the various categorical institutes of the National Institutes of Health and the Alcohol, Drug Abuse, and Mental Health Administration. During Fiscal Year 1989, 19 first- and second-year PRAT fellows worked in 17 different laboratories in 8 different institutes. The goal of this program is to develop topflight leaders in pharmacological research who will take key positions in academic, industrial, and governmental research laboratories. The program is intended for those who have made a commitment to pharmacology through their previous training or research activities, and for those with backgrounds in clinical medicine or basic science who wish to acquire specialized experience in the field of pharmacology.

The PRAT Program was established in 1965, and in the 24 years of its existence, 230 scientists have graduated from the Program. Of those, it is known that at least 204 (89 percent) have entered research careers. Of those employed in research, 95 are located at academic or independent research institutions, 79 at NIH or other Federal research facilities, and 30 at various pharmaceutical firms. Almost 40 percent of the PRAT graduates who are engaged in research possess an M.D. degree, indicating that the program has attracted a large number of physicians and directed them into research careers instead of into clinical practice.

The young men and women chosen for this program are selected on the basis of their academic records, demonstrated research interest, and research accomplishments. They receive high-quality postdoctoral research experience under the direction of 120 senior scientists, including Nobel Prize winner Dr. Marshall Nirenberg. In addition, they may take course work in such areas as pharmacokinetics, experimental statistics, medicinal chemistry, human biochemical genetics, and molecular biophysics.

All of these factors have combined to make the PRAT Program widely recognized for its excellence. The PRAT Program provides an opportunity for these fellows to work at the forefront of research in the pharmacological sciences. For example, Dr. Michael Clark, a PRAT fellow in the Laboratory of Dr. Robert Post of the National Institute of Mental Health, has been looking at two different types of receptors in the brain that bind the neurotransmitter, adenosine. To do this, he has used two drugs which are known to block these receptors, carbamezepine (an anti-epileptic drug) and caffeine. Despite the fact that both drugs block adenosine receptors, they have nearly opposite pharmacological effects. Dr. Clark has found that the reason behind this apparent discrepancy is that the two drugs bind to different classes of adenosine receptors in different regions of the brain.

Over the years, the PRAT Program has produced many such leaders in pharmacological research, and its most recent graduates continue to be involved in innovative research having great potential for solving various problems of pharmacologic interest. Indeed, in the last 15 years, 5 former PRAT fellows have won the J.J. Abel Award, the most prestigious award given to young investigators by the American Society for Pharmacology and Experimental Therapeutics. In 1989, Dr. Alfred Gilman, a former PRAT fellow was awarded the Albert Lasker Award in basic biomedical research.

Since 1978, the PRAT Program has made several positions available which are specifically targeted to the area of clinical pharmacology. Applicants for such positions must have the M.D. degree, a minimum of one year of graduate medical training (internship, residency), and a demonstrated interest in a research career in clinical pharmacology. This sub-program offers qualified candidates opportunities for training in research directly related to the distribution, mode of action, metabolism, and excretion of drugs in the human body, and is designed to attract more physicians into what is considered by the Institute of Medicine's Forum on Drug Development and Regulation to be a shortage area.

Rationale for the Budget Request

The 1991 budget estimate for the NIGMS Intramural Research Program is $1,099,000, an increase of $47,000 over the 1990 current estimate. This request will provide support for a total of 22 PRAT fellows. It is the intent of the Institute to keep this a small program, but one of the highest quality.

National Institute of General Medical Sciences

Research Management and Support

Authorization: Indefinite.

Budget Authority:

1990 Appropriation		1991 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA
151	$22,855,000	154	$23,970,000	+3	+$1,115,000

Purpose and Method of Operation

This activity provides funds for salaries, equipment and supplies, and other administrative costs associated with the professional and support staff of the Institute. In 1991, the Office of the Director will continue to provide the professional leadership and guidance needed to manage the programs of NIGMS. This Office evaluates research needs and selects promising research areas for new or expanded investigation. The Office also maintains contact with the members of the scientific community and of the public through the regular dissemination of information pertinent to their concerns.

The staff in the various program areas will provide the scientific direction and administrative support required for the approximately 4,257 grants and 7 research and development contracts to be funded by NIGMS in 1991. Staff members will manage grant-supported programs; coordinate peer review of competing grant applications for scientific merit and program relevance; serve as contacts for investigators, applicants, grantees, advisory groups, and other components of the NIH, PHS, and other organizations; and compile and report scientific and fiscal information relevant to grant programs.

This activity also supports: (1) services provided centrally by NIH organizational units which do not receive direct appropriations, such as the Division of Research Grants; (2) program evaluation studies; and (3) the National Advisory General Medical Sciences Council.

Rationale for the Budget Request

The 1991 budget request for Research Management and Support is $23,970,000, a net increase of $1,115,000 over the 1990 estimate. This increase represents funds required to support administrative cost increases and the administrative aspects of the Minority Biomedical Research Support Program, which was transferred from the Division of Research Resources on October 1, 1989, and is added to the NIGMS budget request this year.

During 1991, continued emphasis will be placed on management reforms and the streamlining of administrative procedures to effectively carry out the Institute's mission.

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Detail of Permanent Positions

	1989 Actual	1990 Appropriation	1991 Estimate
ES-5	1	1	1
ES-4	3	3	3
ES-1	2	3	3
Subtotal	6	7	7
GS/GM-15	11	12	12
GS/GM-14	19	22	22
GS/GM-13	8	10	11
GS-12	15	16	16
GS-11	3	5	5
GS-10	1	1	1
GS-9	5	6	6
GS-8	9	10	10
GS-7	20	22	23
GS-6	11	12	12
GS-5	13	14	15
GS-4	9	10	10
GS-3	1	2	2
Subtotal	125	142	145
Grades established by Act of July 1, 1944, (42 U.S.C. 207):			
Director Grade			
Senior Grade	1	1	1
Subtotal	1	1	1
Total permanent positions	132	150	153

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

New Positions Requested

	1991		
	Grade	Number	Annual Salary
NIGMS Research Management and Support			
Health Science Administrator............	GS-13	1	$44,092
Grants Technical Assistant..............	GS- 7	1	20,902
Grants Clerk............................	GS- 5	1	16,876
		3	81,870

NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Advisory and Assistance Services

For FY 1991, the Advisory and Assistance Services budget will be $133, the same level as FY 1990. These funds will continue to support a variety services that are essential to the effective development and monitoring of existing programs. Services and studies included in the above categories a support for working groups to provide scientific oversight of GenBank and t Cell Bank; support for Women's Health Initiative; support for both the Mino Access to Research Careers Program and the Minority Biomedical Research Sup Program and support for the National Advisory General Medical Sciences Coun

With the exception of the mandated Council activity, which must be performed by outside experts pursuant to law, the remaining activities noted a require the special scientific expertise and sensitive outside perspectives that representatives of the scientific community can bring to such activiti In addition, these are, by and large, time-limited activities for which it would either be difficult or inappropriate to hire federal employees to perform.

The Institute requires that each request for professional services, as well as other contracts and purchase orders, be approved by the Director, N or the Executive Officer, NIGMS, as the applicable delegations of authority specify. These approvals must be secured prior to the request being proces by the Administrative Office staff. The Director, NIGMS, and the Executive Officer, NIGMS, examine each request carefully for its appropriateness and adherance to regulations, including conflict-of-interest rules. Any contra issued through the Delegated Procurement authorities by the Administrative Office, NIGMS, conform to all applicable regulations, including those deali with a drug-free workplace, with the applicability of GAM 8-15 and Circular 120, and with avoiding use of contracts to substitute for hiring government personnel. All persons involved in the Administrative and Executive Office have received training in procuring such services, and regularly read NIH issuances and other updates or new regulations bearing on these activities.

WITNESSES

	Page
Alberts, Dr. W.W	1003
Amoruso, P.D	249
Baldus, A.C	1003
Berkowitz, S.J	1129
Bick, Dr. K.L	1
Broder, Dr. Samuel	249
Cassman, Marvin	1303
Cohen, Dr. Lois	745
Cyphers, D.F	855
Diggs, Dr. J.W	1129
Fauci, Dr. A.S	1, 1129
Ficca, S.A	539
Fitzsimmons, W.T	1303
Goldrich, M.I	1129
Goldstein, Dr. Murray	1003
Gorden, Dr. P.E	855
Hartinger, J.P	249
Hodgkins, G.E	1303
Kirschstein, R.L	1303
Laurence, L.E	855
Lee, Dr. L.M	1
Lenfant, Dr. Claude	539
Littleton, Dr. P.A., Jr	745
Loe, Dr. Harald	745
Mahoney, J.D	1
Notkins, Dr. A.L	745
Packard, Dr. Barbara	539
Raub, Dr. W.F	1, 249, 539, 745, 855, 1003, 1129, 1303
Roper, Dr. Maryann	249
Shafer, W.S	1303
Sherbert, R.L	1003
Taylor, E.S	745
Wehling, James	539
Williams, D.P	1, 249, 539, 745, 855, 1003, 1129, 1303

INDEX

National Cancer Institute Page
- 1989 TAPS 249
- Accomplishments 302
- ADA Bill 358
- Additonal Funds 376
- AIDS 355
- Anti-Smoking Campaign 314
- Authorization 346
- AZT 302
- Breast and Cervical Screening 282
- Breast Cancer 252
- Breast Cancer Education 306, 381
- Budget Reductions 364
- By-Pass Budget 303
- Cancer and Older Americans 279
- Cancer Centers 400
- Cancer Education 269, 276, 283, 300, 331, 348, 367
- Cancer Education and Training 269
- Cancer Incidence and Mortality 271
- Cancer Prevention 252
- Cancer Prevention Scholars Program 251
- Cancer Research Supported by Private Sector 350
- Cancer Statistics 300
- Cancer Statistics for the Period 1971-1990 389
- Cancer Vaccines 264
- Cathepsin-D 308
- Cervical Cancer 299
- Chemotherapy Dosage 341
- Chernobyl 374
- Children's Inn 405
- Chronic Fatigue Syndrome 346
- Clinical Trials 399
- Clinical Trials Accrual 330, 342, 348
- Community Clinical Oncology Program 354
- Construction 271
- Construction Funding 286
- Curriculum Vitae 322
- Diet and Cancer 259
- Diet Fit 383
- Diet Intervention 378
- Downward Negotiations 377
- Downward Negotiations for Centers 275
- Downward Negotiations of Grants 277
- Drug Labelling Procedures 294
- 366

Page

National Cancer Institute—Continued

Early Detection 287
Earmarks 288
Efforts in Early Diagnosis and Screening for Breast Cancer 296
Extramural Construction 300
Fluoride 319, 360
Foundation Stones of NCI 250
Frederick Cancer Research Facility 287
Gene Cloning 290
Gene Therapy 340
Gene Transfer Therapy 292
Gene Transfer Therapy and Cancer Treatment 292
Genitourinary Cancers 399
Geographic Variations of Cancer 318
Grant Paylines 274
Hemophilia 396
Heredity and Colon Cancer 397
Information Dissemination 271
Information Services 270
Insights into Cancer Metastasis 316
Institute of Medicine Report 276
Institute Priorities 376
Insurance Payment Denial for Breast Cancer Drug Treatment 364
International Activities 266, 281, 356
International Collaboration 386
International Use of PDQ 339
Mammography Training 267
Minority Health Issues 332
Mortality Rates for Rich and Poor Americans 362
Multidrug Resistance 327
NCI—AIDS: AZT and ddI 393
NCI's Toll-Free Hotline 320
NCI/FDA Joint Fellowship Program 328
Neurofibromatosis 322
New Emphasis 265
New Investigations 263, 284
Novel Compounds 404
Nutrition and Cancer 311
Obstacles to Clinical Trial Enrollment 353
Oncogene Research 324
Ovarian Cancer 310
Pancreatic Cancer 317
Pap Smears 402
Pediatric AIDS 293, 343, 352
Personal Services Costs 303
Photodynamic Therapy 278
Polymerase Chain Reaction 289
Prevention Activities 288
Professional Judgment 277
Professional Judgment Budget 286, 351
Progress Against Mortality Rates 261
Prostate Cancer 290
Proton Beam Research 277
Public Health Initiatives 288

National Cancer Institute—Continued Page
Recent Accomplishments 250
Reprogramming 286
Rising Incidence Rates 266
Risk Factors for Breast Cancer 295
State and Local Health Departments 351
Statement of the Director 254
Survival Rates 262
Targeting Prevention Programs 363
Top Recipients of NCI Funds 304
Training Opportunities 285
Treatment Advances 252
Tropical Plant Collection/Drug Development 391
Tropical Plants for Drug Development 280
Underserved Populations 369
Unfunded Construction Projects 302
Women in Research 368
Year 2000 Goal 262

National Heart, Lung, and Blood Institute 539
Achievements in Heart, Lung, and Blood Research 559
Alpha-1-antitrypsin Deficiency 605
Appropriations 560
Artificial Blood 614
Artificial Heart Program 589
Artificial Lung Devices 613
Asthma 569, 601
Asthma Education Program 653
Asthma Program 598
Award Rates 560
Bone Marrow Research 555, 665
Bone Marrow Transplantation 570
Bronchopulmonary Dysplasia 603
Cardiac Arrhythmias 605
Cardiac Energetics 578
Cardiac Risk Factors for Older Patients 602
Cardiac Surgery Unit 561, 651
Cardiovascular Disease and Minorities 655
Centers Program 618
Cholesterol Education Program 591, 597
Cholesterol Measurements 616
Chronic Obstructive Pulmonary Disease 654
Clinical Trials 600, 632
Cooley's Anemia 567
Construction 601
Construction Grants 610, 650
Coronary Bypass Surgery and Angioplasty 591
Cystic Fibrosis 620, 647
Deep Vein Thrombosis 648
Demonstration and Education Research 573
Diet and Children 617
Drugs Toxic to the Heart 622
Education Programs 609, 624, 636
FDA and Food Labeling 588

Page

National Heart, Lung, and Blood Institute—Continued

Framingham Heart Study 569
Glutathione and AIDS 604
Health Promotion and Disease Prevention 572
Healthy Diet for Young American Males 659
Hemophilia 611
Hemophiliacs and AIDS 660
Hepatitis C 614
Hypertension 596, 610
Intramural Research 600
Intramural Research Budget Increase 560
Kawasaki Disease 619
Life-style and Clogged Arteries 612
Lost Opportunities 645
Minority Investigators 626
Minority Related Research 624
National Asthma Education Program 568
National Marrow Donor Program 595, 623, 661
National Marrow Donor Registry 553
PCR Technology 607
Pediatric AIDS 587, 638
Pediatric Cardiology 616
Prevention Activities 600
Primary Pulmonary Hypertension 604
Priority Areas for Additional Funds 579
Professional Judgment Budget 646
Research Career Awards Program 649
Research Centers 582, 630
Research Grants 629
Research Training 594, 599
Rheumatic Heart Disease 619
Sarcoid and the Heart 621
Sickle Cell Disease 627
Sickle Cell Research Centers 571
Staffing Levels 598
Stroke Belt Initiative 623
TPA vs Streptokinase 608
Unmet Needs 598
Uses for Additional Funds 638
Women and Heart Disease 658

National Institute of Allergy and Infectious Diseases **1129**
Accelerated vaccine development 1196
Access and effectiveness 1218
AIDS allocation 1156
AIDS and sexually transmitted diseases 1163
AIDS clinical trials 1158
AIDS education effectiveness 1216
AIDS outreach and technology transfer 1181
AIDS research centers 1172
AIDS vaccine 1170, 1176, 1184, 1205
AIDS 1172, 1217
Asthma in urban minority populations 1167
Award rates 1161, 1186

National Institute of Allergy and Infectious Diseases—Continued Page

AZT
Basic research on AIDS 1170
Bone marrow transportation 1180
Centers for AIDS research 1168
Chronic fatigue syndrome 1179
Clinical trials 1171, 1184, 1222
Controlling cost of AIDS drugs 1170, 1188
Dideoxyinosine (ddI) 1164
Disease funding 1162
Downward negotiations for research centers 1172
Downward negotiations 1188
FTEs 1187
Genetic sequencing 1192
Gorgas Memorial Laboratory 1180
Hemophilia related AIDS 1159
Hemophilia 1209
Hepatitis C 1204
HIV-2 1174
Impact of AIDS on other research programs 1161
Increase in grant applications 1160
Influenza research 1159
International AIDS 1206
Intramural research 1174
Lyme disease 1159
Minorities and AIDS 1185, 1211, 1225
Mouse model 1165
Mycoplasma 1158
National cooperative drug discovery groups 1163
Neurological complications of AIDS 1178
New and competing research grants 1166
NIH AIDS reagent repository 1186
Opening statement 1181
Payline percentile 1130
PCR technique 1186
Pediatric AIDS 1177
Pediatric clinical trials 1157, 1166, 1171, 1183, 1209
Pertussis vaccine 1167
Priority scores 1163
RAG-1 1186
Research centers 1164
Research initiatives 1158, 1188
Research programs 1194
Research project grants 1224
Research training 1187
Sexually transmitted diseases 1192
Sexually transmitted disease research centers 1197, 1214, 1226
Tropical diseases research 1171
Tropical diseases 1171, 1207
Use of additional funds 1224
Vaccines 1194
Women in research 1213, 1224
1220

Page
National Institute of Dental Research 745
AIDS 772, 799, 805
AIDS, pediatric 759
AIDS research, new findings in 784
Animals in research 788
Artificial saliva 772, 788
Budget priorities 755
Budget request, increase over 798
Cancer therapy, oral complications of 781, 783
Chronic facial pain 772
Cleft lip and palate 758
Clinical trials 763, 795, 803
Dental implants 767, 777
Dental sealants 773
Dental X-rays, use of 760
Dentist-Scientist Program 768, 802
Diabetes, dental disease and 779
Diagnostic marker for HIV in saliva 759
Downward negotiations 765, 793
Economic savings, NIDR involvement in 762
Ectodermal dysplasia 758
Fluoride controversy 755
Fluoride, toxicology studies on 761
Grants, effect of decreasing numbers of 793
Grants, judging quality of 769
Improvements in dental health 770
Infectious diseases 774
Long-range research plan 754, 786, 792
Mercury amalgams 766
Minorities, attracting into dental research 760
Minorities, oral health in 759
Minorities, oral health problems in 785
Minorities, oral health status among 787
Mission, broadening the NIDR 754
Muscle regeneration 764
Muscle repair and transplantation 764
National Toxicology Program data on fluoride 756
Opening remarks 745
Oral health and other disease 806
Oral health initiatives 745
Pain research 789
Percentiles and award rates 793
Reconstructive surgery 783
Research and action program 757, 807
Research centers 766, 794
Research centers, dental clinical 802
Research centers, materials science 764, 797
Research training, dental 780
Restorative materials 772
Saliva and HIV 761
Saliva testing 767
Smokeless tobacco 776
Special care patients 787, 791

National Institute of Dental Research—Continued Page
Statement of the Director
Taste and smell ... 747
TMJ-related disorders ... 776, 788
Toxicology data, review of ... 769. 779, 800
756

National Institute of Diabetes and Digestive and Kidney Diseases ... 855
Accuracy of Sugar Tests ... 902
AIDS Research ... 899
Amyloid and Diabetes ... 901
Bladder Disease ... 932
Clinical Trials ... 915
Complications of Diabetes ... 927
Cooley's Anemia ... 878
Cystic Fibrosis ... 881, 918
Cystic Fibrosis Projects ... 884
Cystic Fibrosis Testing ... 929
Diabetes ... 879
Diabetes and Pregnancy ... 898
Diabetes and Related Research Spending Table ... 875
Diabetes Budget ... 872
Diabetes Control ... 896
Diabetes Gene ... 872
Diabetes in Minorities ... 925
Diet and Renal Disease Trial ... 888
Digestive Diseases Advisory Board ... 896
Digestive Diseases Centers ... 895
Downward Neogtiation of Grants ... 884
Fetal Tissue ... 934
DRG Study Section ... 931
Future Direction in Research ... 871
Genetic Research ... 871
Genetically Engineered Insulin ... 926
Graves' Disease ... 904
Hepatitis C ... 894
Implantable Insulin Pump ... 920
Insulin Pumps ... 926
Interstitial Cystitis ... 888, 917
Justification of the Budget Estimates ... 936
Kidney Diseases ... 902
Kidney Disease of Diabetes Mellitus ... 877, 917, 924
Liver Transplantation ... 897, 911
Liver Transplants ... 885
New Immunosuppressive Drug ... 892, 920
New Initiatives in 1991 ... 921
Number of Grant Applications ... 888
Obesity ... 899
Opening Remarks ... 855
Osteoporosis ... 928
Parathyroid ... 905
PCR Technique ... 892
Photographs of Charts (7) ... 858
Polycystic Kidney Disease ... 893

Page

National Institute of Diabetes and Digestive and Kidney Diseases—Continued

Priorities for 1991 ... 923
Prostatic Disease ... 901, 931
Purine Drug Therapy ... 891
RDA Allowances ... 895
Research Centers ... 882, 910, 914
Research Grants ... 913
Research on Steroids ... 920
Research Training ... 890
Role of Diet in Kidney Failure ... 910
Sickle Cell Anemia ... 911
Statement of the Director ... 865
Training in Nephrology Research ... 876
Ulcers ... 891
Undiagnosed Diabetics ... 919, 924
Urological Cancers ... 933

National Institute of General Medical Sciences ... 1303
Attracting young people into science ... 1318
Biophysics and physiological sciences ... 1394
Biotechnology ... 1312, 1331, 1345
Cell bank ... 1316
Cell cycle control ... 1315
Cellular and molecular basis of disease ... 1341, 1380
Diagnostic Imaging ... 1329
Downward negotiations ... 1343
Genbank ... 1328
Genetics ... 1327, 1334, 1338, 1384
Goals for MARC and MBRS programs ... 1319
Grant award funding guidelines ... 1323
Grant award supplements for minority investigators ... 1337
Immunogenetics ... 1348
Immunosuppressant drugs ... 1351
Importance of basic research ... 1332
Intramural research ... 1406
Lost research opportunities ... 1346
Medical scientist training program ... 1313
Minorities and women in science ... 1317
Minority access to research careers program ... 1333, 1401
Minority biomedical research support program ... 1325, 1333, 1398
Minority programs ... 1321
National academy of sciences research manpower report ... 1310
National biotechnology policy board ... 1321
National center for biotechnology information ... 1351
National center for human genome research ... 1350
Number of predoctoral trainees ... 1312
Opening statement ... 1303
PCR reaction ... 1314
Pharmacological sciences ... 1389
Physician-researcher training ... 1325, 1345
Plan to assist new investigators ... 1330
Rational drug design ... 1336

Page

National Institute of General Medical Sciences—Continued
Receptor research 1329
Research center grants 1325, 1343
Research management and support 1408
Research payoffs 1329
Research trainee stipends 1321
Research training 1310, 1331, 1333, 1344
Ribozyme and chemzyme research 1315
Scanning tunneling microscope 1315
Structural biology research 1340
Support for basic research 1314
Support for research in chemistry 1348
Support for research project grants 1342
Training period for research scientists 1321
Use of additional funds 1346

National Institute of Neurological Disorders and Stroke 1003
Additional funds 1060
Advertising unfunded projects 1022
AIDS and neurology 1046
AIDS dementia 1069
Alzhiemer's disease 1049
Balance between grants 1017
Batten's disease 1072, 1050
Brain damage in children 1068
Brain injury, acute 1008
Budget estimates, Justification of the 1076
Clinical research 1059
Clinical trials 1048, 1058
Cognition research 1020
Children with neurological AIDs 1038
Chronic fatigue syndrome 1074
Cost of major neurological disorders 1065
Decade of the Brain 1003, 1064
Disease expenditure estimate 1044
Downward negotiations 1015, 1039
Dystonia 1047, 1074
Epilepsy 1070
Fetal tissue 1019
Funding for new research initiatives 1060
Gaucher's disease 1004, 1042
Grant applications 1018
Grant ceiling impact 1047
Grants, new and competing 1052
Head injury 1021, 1068
Head injury and spinal cord injury 1064, 1070
Human genome project 1049
Huntington's disease 1042, 1063, 1048
Javits awards 1018
Joseph disease 1066
Laser treatment of stroke 1038
Magnetoencephalography 1034
Multiple sclerosis 1034, 1065
Muscular dystrophy 1034

Page

National Institute of Neurological Disorders and Stroke—Continued
- Narcolepsy 1037
- Nerve pacemakers 1045
- Nerve regeneration and growth 1046
- Neurofibromatosis 1021, 1022
- Neurological implications of crack 1037
- Newborn brain hemorrhage/low birthweight 1051
- Parkinson's disease 1045
- Parkinson's disease/fetal tissue research 1074
- PCR Technique 1034
- Positron Emission Tomography (PET) centers 1019
- Professional judgment budget 1062
- Research career awards 1059
- Research centers 1017, 1041, 1051, 1052
- Research management and support 1017
- Research priorities 1017, 1018
- Research Trainees 1063
- Sequestration 1035
- Sleep disorders/narcolepsy 1075
- Sleep research 1037
- Statement of the Director 1011
- Stroke 1035, 1051
- Traumatic brain injury 1068
- Women in research 1072

Overview 1
- ACTG Trials 123
- Agency for Health Care Policy and Research 105, 164
- AIDS 31
- AIDS vs. Non-AIDS Funding 61
- AIDS Budget Chronology 170
- Air Quality Study 106
- Animal Welfare and Terrorism 40
- Animal Welfare 35
- Animal Facilities 89
- Animals in AIDS Research 36
- Average Costs of Grants 46, 57
- AZT and DDI Trials 201
- Biomedical Research Training Programs 164
- Bone and Mineral Disease 208
- BRSG Program 147, 171
- Budget Increases 167
- Budget Priorities 71
- Budget Reductions 32
- Building and Facilities 51, 60
- Child Immunization 172
- Child Health and Neurosciences Building 107
- Chronic Fatigue Syndrome 91, 198
- Chronic Diseases 182
- Chronology of the FY 1991 Budget 131
- Clinical Center 93
- Clinical Trials 59, 93, 153
- Conflict of Interest 33, 105
- Construction 84

Overview—Continued Page

Cooperative Research and Development Agreements 60
Cost of Awards 110
Current Services 9
Cystic Fibrosis 2
Decade of the Brain 97
Decentralization 65, 70
Diagnostic Radiology Laboratory 111
Director's Discretionary Fund 97
Director's Discretionary Fund and Transfer Authority 88
Director's Statement 4
Disease Prevention 30
Disease Treatment 208
Downward Negotiations 43
DRR Reorganization 34
Drug Development 118
Employees Earning More than the NIH Director 52
Endowed Research Chairs 64
Extramural Construction 69, 110, 166
Extramural Pay Cap 32
Federal Technology Transfer 189
Fetal Tissue 179, 192
Funding History 10
FY 1991 Budget Formulation Process 130
FY 1991 Budget Increases 9
FY 1991 Budget Request 3
Genome Project 85
Grant Approval Rates 47
Grant Review Process 47
Health and Behavior 176
Health Care Costs 58
Hepatitis 206
Historical Cost of Grants 46
Human Genome 33
Human Genome Information 178
Human Genome Project 108
Hypertension 207
Increase in Average Cost of Grants 46
Increases in Average Cost 129
Indirect Costs 48, 89
Infant Mortality 30
Inflation Factors 128
Institutional Recipients 93
International AIDS Effort 68
International Research 67
Intramural Research 86, 95
Intramural Program 203
Justification of the Budget Estimates 212
Length of Grants 29
Lyme Disease 205
Major Scientific Breakthroughs 53
Minorities in Management 56
Minority Howard Hughes Research Scholars 55
Minority Scientists in Extramural Research 54

Page
Overview—Continued
Minority Scientists on Intramural Research 55
Minority Programs 34
Minority Recruitment 56
National Biomedical Priorities 65
National Center for Nursing Research 31
National Institutes of Health (Intramural Animal Facilities) 89
NCBI Computer Support 178
NCBI Service Access 179
New Institutes 9, 66
NIH Director 8, 52
NIH Budget Request 43
NIH Supported Research 183
Nobel Laureates 48
Object Classification 91
Office of Scientific Integrity 188
One Percent Set-Aside 125
One Percent Transfer Authority 126
Opening Remarks 1
Opportunistic Infections 116, 170
Pay Raise 153
Peace Dividend 29
Pediatric AIDS 98
Pediatric AIDS Funding 95
Polymerase Chain Reaction 106
Premature Deaths 182
Private vs. Public Funding 8
Professional Judgement Budget 167
Program Evaluation Expenditures 163
Quality of Research Applications 147
Reproductive Health 173
Research Agreements with Eastern Bloc 67
Research Careers 54
Research Training 61
Research Project Grant Awards 58
Research Project Grants 82, 103, 109, 131, 147, 171, 187, 194
Salaries 51
Salary Cap 96
Senior Biomedical Research Service 97
Senior Scientists 112
Sequester 103
Sequestration 153
Set-Aside Account 105
Staffing 63
Statistical Data—Research Grants 90
Stipend Levels 165
Training 83
Unauthorized Activities 96
Women in Research 175

○